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SURGERY

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SURGERY

VOL. 33 JANUARY, 1953 No. 1

Original Communications

AN EVALUATION OF THE BILLROTH I OPERATION FOR PEPTIC ULCER

STEN WALLENSTEN, M.D., AND LARS GÖTHMAN, M.D., FALUN, SWEDEN

(From the Surgical Department, Lasarettet, Falun, Sweden)

DURING the past two decades surgical treatment for the relief of peptic ulcer has become increasingly popular in Sweden owing to the steady decline in the mortality rate of partial gastrectomy as well as to increased operative experience and a better understanding of gastric physiology.

Experimental and clinical studies (Mann and Williamson,[22] Matthews and Dragstedt,[23] Wangensteen and associates[42, 43]) have shown that a peptic ulcer depends to a considerable extent on the precedent history of gastric acidity. Therefore our surgical effort is directed toward the reduction of the gastric acidity in addition to the removal of the ulcer.

It has been proved by experience that the best results are afforded by partial gastrectomy. This procedure, in which the entire pyloric region is removed, completely eliminates the gastric phase of the secretion (Edkins,[7] Komarov[18]). The cephalic phase is also reduced, which fact was experimentally demonstrated by Uvnäs,[39, 40] and later also clinically by Noring[25] and Velander.[41] It would appear that the removal of at least 60 per cent of the stomach is necessary to obtain satisfactory results.

The procedure most frequently employed is a modified Billroth II type of operation, because the Billroth I type, although better from a physiologic standpoint, is not considered to be sufficiently radical. Only a few surgeons in this country have adopted the latter as the standard technique, chief among them being Bohmansson[2, 3] whose initial and late results have been gratifying.

One of the difficulties encountered after operation, the so-called dumping syndrome, has, however, led to considerable discussion in recent years regarding the best surgical procedure for the lesion in question. Both experimental (Hertel,[13] Spath,[38] and others) and clinical (Bohmansson[2, 3] Higginson and Clagett[14]) investigations have shown that the physiologic end results of the Billroth I operation are better than those of the Billroth II. Perman[31] also recommended conversion to Billroth I in all cases in which pronounced dumping had followed Billroth II, leading to complete invalidity.

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Reports of the late end results of the Billroth I operation have been few and far between, and in many instances based on small materials (Bohmansson,[2, 3] Pettersson,[32] Jonsson,[17] Perman,[29, 30] von Haberer,[11] Higginson and Clagett,[14] Odelberg[27]). In a monograph published in 1950 the authors (Ivy, Grossman and Bachrach[16]), while pointing out the superiority of the Billroth I technique from a physiologic standpoint, raised the question of the late results of the procedure in ulcer patients in order to be able to draw definite conclusions regarding its effectivity and advantages. The present study, therefore, represents an attempt to answer these questions on the basis of our own past experience.

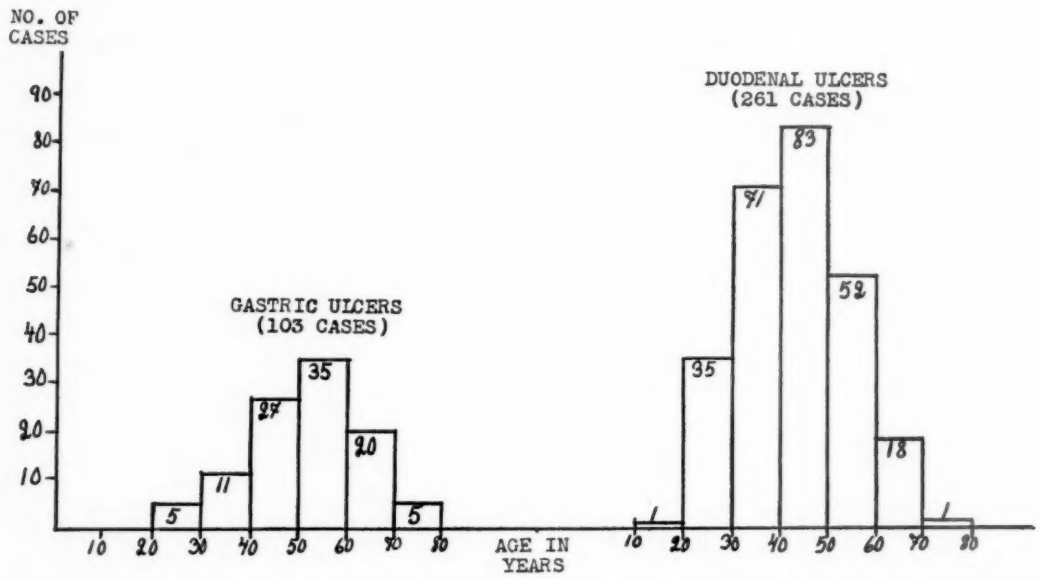

Fig. 1.—Age distribution of patients with gastric and duodenal ulcers.

CLINICAL MATERIAL

The present series consisted of 364 patients (250 men and 114 women) with peptic ulcers who were submitted to the Billroth I operation; 321 at the Falun Lasarett during the years 1932 to 1949, and 43 at the Mora Lasarett during the years 1938 to 1948. Of this number 261 patients (184 men and 77 women) had duodenal ulcers (9 of them both duodenal and gastric ulcers) and 103 (66 men and 37 women) only gastric ulcers. The age distribution of the two groups is shown in Table I, and graphically presented in Fig. 1. The youngest patient was 18 years of age and the oldest 76 years. In the gastric ulcer group 71 per cent of the patients were over the age of 50, while in the duodenal ulcer group the figure was 40 per cent. The higher average age of the gastric ulcer patients in this series is in conformity with published reports.

In assessing the value of the Billroth I operation in the treatment of duodenal ulcers the factors of prime importance are the location of the ulcer and the depth of penetration. As seen in Table II, in no less than 40 per cent of the patients in this series the ulcer had penetrated to the pancreas, thus rendering mobilization of the posterior wall of the duodenum relatively difficult.

Perman[29] found that the acidity of the gastric juice in ulcer patients varied considerably in different parts of the land. He reported that in Stockholm the average total acidity was much higher than, for example, in Umeå. In the present series, the major part of which came from Dalecarlia, the average total acidity followed more closely that of ulcer patients in the province of Norrland (Table III and Fig. 2). These values are, however, given with guarded reservation owing to the drawbacks of the method used in the investigation of the gastric secretion (Ewald's test meal).

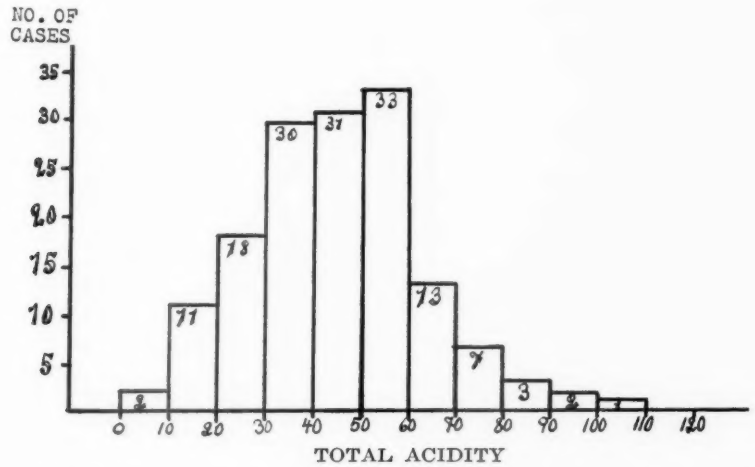

Fig. 2.—Preoperative total acidity by Ewald's test meal (153 cases).

INDICATIONS FOR OPERATION

As far as peptic ulcer was concerned, the indication for operation was often relative, and persistent failure to yield to conservative treatment frequently constituted the indication for operation. The deciding factor was generally the degree of invalidity that was caused, and the decision usually rested with the patient. In duodenal ulcer, on the other hand, more importance was attached to the roentgenologic evidence of bulb deformity, the indication for operation being the amount of obstruction demonstrated. According to Perman[30] healing conditions in the duodenum in the presence of a bulb deformity are poor, and consequently recurrences are frequent. Therefore, in spite of a relatively short clinical history and only one or two periods of dietary management, surgical intervention was considered justified, even if the roentgenogram showed no evidence of a crater niche. In recent years there has been a tendency to undertake surgery for gastric ulcers at an early stage, especially in elderly individuals, because of the ever present danger of potential carcinoma. Absolute indications for surgical treatment were stenosis, probable carcinoma, and massive hemorrhage. There were four instances of emergency surgery for acute massive hemorrhage in this series, one of which ended fatally. Most patients with only relative indications for surgical treatment received intensive dietary and medical management before being advised to accept surgical therapy. The duration of the ulcer histories is shown in Table IV.

TABLE I. AGE DISTRIBUTION IN PEPTIC ULCERS

AGE	GASTRIC ULCER	DUODENAL ULCER	TOTAL
10 to 19	–	1	1
20 to 29	5	35	40
30 to 39	11	71	82
40 to 49	27	83	110
50 to 59	35	52	87
60 to 69	20	18	38
>69	5	1	6
Total	103	261	364

TABLE II. DISTRIBUTION OF DUODENAL ULCERS (260 CASES)

ANTERIOR WALL	POSTERIOR WALL		KISSING ULCERS	
	PENETRATING	SUPERFICIAL	PENETRATING	SUPERFICIAL
99	74	7	32	48
38%	28.5%	2.7%	12.3%	18.5%

TABLE III. RELATION OF GASTRIC ACIDITY TO DOMICILE

SOURCE	METHOD	NUMBER OF CASES	UNITS OF TOTAL ACID PER 100 C.C.		
			<40	40 TO 60	>60
Stockholm, Perman	Ewald	241	21.9	32.5	45.6
Sala, Hedlund	Ewald	149	19.4	37.0	43.6
Umeå, Bohmansson	Ewald	71	42.3	38.1	19.7
Falun, Wallensten	Ewald	153	39.9	41.8	17.0

TABLE IV. DURATION OF ULCER HISTORY (359 CASES)

DIAGNOSIS	DURATION OF ULCER HISTORY IN YEARS				
	<6	6 TO 10	11 TO 20	>20	TOTAL
Gastric ulcer	42	32	22	6	102
Duodenal ulcer	98	83	57	19	257

OPERATIVE TECHNIQUE

The resection technique employed was that recommended by Bohmansson,[2, 3] with the upper resection border running parallel to the circular muscle layer in order to guard against postoperative impairment of gastric motility. It was decided to remove two-thirds of the stomach in all cases. The upper incision was started at a point approximately 2 cm. above the point at which the branches of the right gastroepiploic artery stop short (sometimes slightly higher) where there is a small area free from blood vessels. After the method of Bohmansson, no clamps were applied to the portions of stomach and duodenum to be conserved. Careful mobilization of the duodenum with Kocher's technique was carried out as a prophylactic against tension in the anastomosis, and did not as a rule cause any great inconvenience. The anastomosis was closed in two layers; one of continuous catgut sutures posteriorly and anteriorly, and a second of interrupted catgut serosal sutures. Before further closure the operation area was carefully dried with a 3 per cent hydrogen peroxide solution, a little of which was also left in the abdominal cavity. The abdominal wall was sutured in two layers; the fascia with catgut and the skin with continuous silk.

Various types of anesthesia were given a trial—ether supplemented by local, spinal supplemented by local, ether with narcotal, and, during the past two years, a narcotal-nitrous oxide-oxygen-curare mixture.

PRE- AND POSTOPERATIVE TREATMENT

The preoperative condition of all patients was very carefully investigated, in the first part of the investigation chiefly in regard to anemia and the general nutritional state. More recently, this was complemented with control and correction of fluid balance and hypoproteinemia. Anemia was treated with intravenous blood and plasma, and aminosol preparations. Efforts were made to give the patients a liberal diet and, if there was vitamin deficiency, additional supplementary vitamins, especially B and C, since the diet had usually been rather monotonous. No patient was submitted to operation until his general condition was as satisfactory as possible.

Postoperatively the aim was to keep the electrolytic fluid therapy at a minimum. During the first few days following operation even a slight fluid deficit was permitted, in order to control the tendency to edema at the site of the anastomosis with its attendant emptying disorders (Sandberg[36]). In uncomplicated cases 1,000 ml. of physiologic saline was administered subcutaneously on the day of operation, and 2,000 ml. of saline with glucose on the two following days. In recent years dextran solution has replaced normal saline on the day of operation. On the day following operation the patients were permitted to drink up to 600 ml. of fluid in the form of fruit juices, soup, and similar foods, and on the following days the quantity was fairly rapidly augmented. A duodenal tube was used only if there were signs of retention, and not as a prophylactic. The patients were generally out of bed on the first postoperative day and were allowed to sit up in a chair during some part of the following days.

This early ambulation was instituted not only to guard against thrombosis but also because the upright position facilitates satisfactory emptying of the stomach. Where there had been preoperative or surgical shock, however, blood transfusions and, in recent years to a greater extent, intravenous dextran were administered.

OPERATIVE MORTALITY AND PRIMARY POSTOPERATIVE COMPLICATIONS

In the 364 cases of resection there were 8 operative deaths, a mortality rate of 2.2 per cent (in the elective resections the mortality rate was 1.9 per cent). Autopsy was performed in each case (Table V). The operative mortality rate for duodenal ulcers was only 1.2 per cent and for gastric ulcers 4.9 per cent (in elective surgery 3.9 per cent). The higher mortality rate for gastric ulcers was probably due to the aforementioned higher average age of the patients.

Hemorrhage following partial gastrectomy is generally due to bleeding at the site of the anastomosis, most frequently from the gastric side, as a result of inadequate ligation or imperfect stitching. Following the Billroth II-Finsterer exclusion operation the source of bleeding may, of course, be the unremoved ulcer. A rare source of hemorrhage following radical resection is

TABLE V. AUTOPSY RESULTS (8 CASES)

HOSPITAL NUMBER	AGE	SEX	DIAGNOSIS	AUTOPSY FINDINGS
554/35	23	M	Duodenal ulcer	Peritonitis; operative region and sutures, no appreciable disease
956/36	41	M	Gastric ulcer	Peritonitis; leaking suture line
1504/38	31	M	Gastric ulcer	Peritonitis; operative region and sutures, no appreciable disease
M 1376/37	50	M	Gastric ulcer	Paralytic ileus
M 1888/38	39	M	Duodenal ulcer	Cardiac disease
383/46	60	M	Duodenal ulcer	Abscesses of liver and spleen
2683/46	56	F	Gastric ulcer	Pulmonary embolus
3594/46	52	M	Gastric ulcer	Pulmonary embolus

an ulcer that has been overlooked. In all published reports the incidence of postoperative bleeding is small; Bruusgaard[5] reported 11 cases in 578 resections and Grevillius[9, 10] 3 cases in 216 resections.

In the present series there were 2 instances of postoperative hemorrhage. One occurred in a woman, aged 32 years, who had been operated upon for two fairly superficial kissing ulcers in the duodenum. During the night following the operation she vomited large quantities of blood and blood clots, which led to profound shock. She rallied, however, after blood transfusions; the bleeding stopped and the blood pressure returned to normal. The remainder of the postoperative course was smooth, and the patient left the hospital on the sixteenth day after operation. The other occurred in a man, aged 43 years, also operated upon for kissing ulcers in the duodenum; the ulcer on the posterior wall had penetrated. A few hours after operation the patient suddenly exhibited symptoms of shock and vomited large quantities of blood and blood clots. On account of the continued shock arterial bleeding was suspected, and a blood transfusion was given preparatory to reoperation. The abdomen was reopened and the anterior line of union broken down, revealing arterial bleeding from the gastric end of the anastomosis. The bleeding was arrested by ligation of the bleeding vessel. The postoperative course then progressed smoothly and the patient left the hospital on the ninth day after operation. He returned, however, a week later with an infected hematoma in the incision area.

Failure of suture is a serious complication and carries a high death rate. It is said to occur fairly frequently, especially following the Billroth I type of operation. In this series it occurred in only one instance and was responsible for the fatal outcome. The patient was a 41-year-old man who had been operated upon for a gastric ulcer about 1 cm. in diameter in the lesser curvature. The usual resection was performed without any technical difficulties. The postoperative course was smooth until the sixth day after operation when there were signs of peritoneal irritation. Relaparotomy on the eighth postoperative day disclosed general peritonitis due to leakage from the anterior line of union and upper angle of the anastomosis. The abdominal cavity was drained, but the patient died from peritonitis on the thirteenth postoperative day.

Two further cases of postoperative peritonitis responsible for fatal outcomes are included in this series. One was a 23-year-old man with a two-year history of duodenal ulcer for which he had had two periods of dietary manage-

ment in the hospital. He had also suffered from severe gastritis. Operation was undertaken on account of the repeated recurrences and the attendant severe pain which the patient found intolerable, although the unmistakable evidence of gastritis was a contradictory factor. The usual resection was performed with no technical difficulties. An ulcer scar was found in the duodenum. but, on the other hand, gross changes occurred in the gastric mucosa which bled more than was normal at resection. The temperature rose sharply (39° to 40° C.) and the pulse rate was greatly increased. In addition, the patient had attacks of excruciating abdominal pain. The day following the operation there were definite signs of peritonitis. A relaparotomy was performed and a fibrinopurulent exudate was disclosed in the wound area. Free drainage was established but the patient's condition rapidly deteriorated and he died the following day. At autopsy a fibrinopurulent peritonitis was found in the operation area, but examination of the gastroduodenal preparation excised in toto showed no leakage from the line of union. There was extreme gaseous extension of the stomach but no escape of bubbles when tested by strong pressure under water. The smell from the emptied gastric contents was, however, the same as that from the peritoneal cavity and therefore the peritoneal infection was considered to be the same as that of the stomach.

The other case was that of a 31-year-old man who for eight years had had continued recurrence of ulcer symptoms which caused only slight disturbances. He had had two periods of dietary management. A further recurrence led to his being admitted for operation. A few hours after admission he had a massive hemorrhage and marked symptoms of shock. His condition improved with blood transfusion. Operation appeared to be indicated, and, since the patient's condition was satisfactory on the day following the hemorrhage, it was decided to perform a resection. At operation the lesser curvature was found to be considerably shortened by shrinkage and only about 9 cm. in length, with two deeply penetrating ulcers, one with a crater 2 cm. in diameter in which could be seen the open lumen of an artery 1 mm. in diameter. The other ulcer was situated near the cardia, also deeply penetrating, and about 1 cm. in diameter. In order to remove the entire infiltrated area it was necessary to make the resection very near the cardia, and during the stitching the two top invagination sutures caught in the cardia. A stomach tube was passed to ensure that the passage into the stomach was not obstructed. A number of inflamed glands were observed in the omentum minus and majus. Following the operation the patient had a rise in temperature, and on the fourth postoperative day there were unmistakable signs of peritonitis. A relaparotomy was performed, disclosing general peritonitis, and the patient died on the following day. Autopsy revealed general peritonitis, but no definite signs of leakage from the line of union.

In the last case the unmistakable evidence of peritonitis on the fourth postoperative day was characteristic of the clinical picture of failure of suture, more so due to the fact that the invagination sutures encroached upon the cardia. At autopsy the anastomosis was not thoroughly examined—there was no testing under water—and it is possible that there was a slight leakage.

The first case, however, is of far greater interest since the line of union was obviously intact, and yet the patient died from peritonitis which undoubtedly had its origin in the stomach. At operation only a healing scar was found in the duodenum, but there was evidence of severe gastritis which was probably the cause of the trouble. The clinical picture resembled that of phlegmonous gastritis, fortunately a rare condition, and probably the cause of the peritonitis. The resection caused a spread of the infection to the surrounding tissues. This case is analogous to a later one operated upon in 1950, in which the diagnosis was verified by histologic examination. The patient was a 40-year-old man with a history of ulcer symptoms for several years. He was admitted to the hospital with high fever and very severe gastric pain. Chemotherapy was instituted to which the symptoms responded. X-ray examination revealed a duodenal ulcer and a severe inflammatory condition of the stomach. When the patient's temperature became normal it was decided to perform a resection for the recurrent duodenal ulcer. The usual resection was performed, and a much altered gastric mucosa and a small duodenal ulcer were disclosed. Immediately following the operation there was a marked rise in temperature, and, despite intensive chemotherapy, peritonitis developed. Reoperation showed a fibrinopurulent peritonitis confined to the operative area, and blood and blood clots in the stomach. The bleeding came from the gastric mucosa which was extremely congested and edematous. Despite treatment the patient died, and at autopsy the diagnosis of phlegmonous gastritis was confirmed.

Gastric retention is the most frequent complication following partial gastrectomy. Various reasons for the phenomenon have been given. Both Perman[29] and Bohmansson[2, 3] drew attention to the possibility of impaired vagal innervation to the gastric remnant, resulting in decreased tonus and motility. Brandberg[4] warned against the danger of overstretching the stomach in the Billroth I operation, and making the jejunal loop too short in the Billroth II operation, leading to tension and paresis in the stomach and consequent delayed emptying. Sandberg[36] stressed the increased susceptibility to stomal edema in the presence of hypoproteinemia as a cause of retention. Wahren[44] stated the opinion that circulatory impairment in the splanchnic area might be the explanation of this so-called gastric ileus.

As regards the treatment of this complication, most authors point out the danger of indiscriminate use of relaparotomy and further anastomosis since in most cases there is no mechanical obstruction and the operation has a high mortality risk. Our present practice, and one which usually achieves good results, is the emptying of the stomach by means of a duodenal tube, often followed by continuous aspiration. Careful control of the fluid balance is of great importance, particularly for control and correction of a hypoproteinemia.

It is generally believed that the Billroth I technique predisposes to a greater incidence of postoperative gastric retention than does the Billroth II. It is therefore of interest to compare the frequency of this complication in the present series with that of other series in which the Billroth II was performed (Table VI).

In this series postoperative emptying disorders occurred in 18 cases. In 5 cases the disorders lasted for less than 4 days. As seen in Table VIII, the

TABLE VI. INCIDENCE OF GASTRIC RETENTION AFTER GASTRECTOMY

MATERIAL	METHOD	NUMBER OF CASES	GASTRIC RETENTION IN DAYS			PER CENT
			<4	4 TO 7	>7	
Hjorth	Billroth II	52	47	3	2	9.6
Olovson	Billroth II	235	219	12	4	6.8
Ringdahl	Billroth II	105	101	4	–	3.8
Rödén	Billroth II	107	96	6	5	10.3
Brandberg	Billroth I + Billroth II	314	289	17	8	8.0
Present series	Billroth I	356	342	7	6	3.7

results obtained with Billroth I as the sole procedure were equally as good as those obtained with Billroth II or Billroth I and Billroth II combined. It is, however, pointed out that in Brandberg's series cases of carcinoma were also included, which accounts for the increased incidence of postoperative emptying disorders. Our good results in this connection would seem to stress the importance of careful attention to the patient's general condition before operation, with carefully controlled electrolyte and colloid fluid balance as well as correction of anemia and vitamin deficiency. Of less importance appear to be the details of operative technique and the different methods of suture used. Effective drainage of the stomach is dependent upon the size of the gastroduodenal stoma in Billroth I and the gastrojejunal stoma in Billroth II. This cannot be larger than the width of the intestine, but may sometimes be smaller, depending on the anastomosis. Our experience supports the view put forward by Sandberg[36] that the main cause of poor gastric emptying is probably edema of the stoma due to excessive fluid therapy, especially electrolytes.

Serious *complications from the biliary tract and pancreas* did not occur in this series. There was, however, no continuous control of the pancreatic function postoperatively, which prevents the forming of any definite opinion regarding the occurrence of postoperative pancreatic irritation.

Complications of a more general nature were relatively few. Wound disruption occurred in 19 cases or 5.4 per cent of the series. Since 1947, with the more thorough study of the blood picture, there has been no case of wound disruption, despite the early ambulation. A temperature of over 38.2° C. on the fourth postoperative day or earlier occurred in only 34 cases. In this number are included pulmonary complications, such as bronchopneumonia and thromboembolism. The conditions responsible for the raised temperature are listed below:

CONDITION	NUMBER OF CASES
Pulmonary complications	16
Thromboembolism	6
Pyelitis	1
Chill with fever, following intravenous drip	1
Polyarthritis	1
Unknown	9
Total	34

If the 2 cases of postoperative death from pulmonary embolism are included, the incidence of thromboembolism becomes 8, or 2.2 per cent.

POSTOPERATIVE DURATION OF TREATMENT

During recent years early ambulation has become more and more strongly advocated. It was not possible earlier when spinal anesthesia was used, but has been made increasingly so by the introduction of combined narcotal-nitrous oxide-oxygen-curare anesthesia.

It was therefore of interest to compare the postoperative duration of treatment for different periods, and to this end the material was divided into two main groups: (1) covering the period 1932 to 1944 and (2) the period 1945 to 1949. This grouping was motivated by the fact that since 1945 new concepts of guiding the fluid therapy have emerged. Group 2 was further divided into two subgroups: (a) the years 1945 to 1947, when spinal anesthesia was used, if necessary complemented by narcotal-nitrous oxide or ether and (b) the years 1948 to 1949, when the sole method of anesthesia was combined narcotal-nitrous oxide-oxygen-curare (Table VII).

TABLE VII. DURATION OF POSTOPERATIVE TREATMENT

PERIOD	NUMBER OF PATIENTS	POSTOPERATIVE TREATMENT (NUMBER OF DAYS)	
		TOTAL	AVERAGE PER PATIENT
1932 to 1944 (1)	219	3,942	18
1945 to 1949 (2)	136	1,507	11
1945 to 1947 (2a)	57	763	13.4
1948 to 1949 (2b)	79	744	9.4

It will be noted by referring to Table VII that the postoperative duration of treatment was reduced by one-half during the latter period (1945 to 1949) by virtue of better pre- and postoperative measures, particularly in regard to maintenance of fluid and electrolyte balance, blood analysis, and chemotherapy. A comparison of the periods 1945 to 1947 and 1948 to 1949 shows that even during this short period there was a considerable reduction of the postoperative duration of treatment, a fact most probably attributable to modern anesthesia which enabled early postoperative ambulation.

LATE RESULTS

The follow-up study was done principally by questionnaires sent out to the patients and formulated as follows:

1. Have you maintained your weight after the operation? What is your present weight? . . . Your normal weight? . . . Your highest weight?
2. Are you able to do full work? . . . If not, what is the percentage of your working capacity? . . . What is the cause of your disability?
3. Are you satisfied with the operation?
4. Have you kept well since the operation?
5. Have you been able to eat unrestrictedly since the operation? . . . If not, what foods do you not tolerate? . . . Why? . . .
6. Is your appetite good?
7. Are you troubled with flatulence?

8. Have you, or have you had, anemia since the operation? . . . Have you noticed blood in the stools? . . . Have you had tarry stools? . . .
9. Do you need to take medicine?
10. Do you feel nervous?
11. Have you been troubled with fatigue, cold sweat, paleness, or abdominal pain after taking a meal?
12. Have you visited a doctor for stomach trouble since the operation? . . . If so, give name of doctor. . . . Have you had an x-ray picture taken of your stomach?

Eight patients who died as a direct result of the operation were automatically eliminated from the follow-up study. Thus questionnaires were sent to 356 patients, of whom 330 or 93 per cent replied. During the follow-up period 35 patients died. The cause of death according to the Death Certificate is given in Table VIII.

TABLE VIII

CAUSE OF DEATH	GASTRIC ULCER NUMBER OF CASES	DUODENAL ULCER NUMBER OF CASES
Cardiovascular diseases	10	7
Gastric carcinoma	3	2
Carcinoma of other localization	1	1
Pulmonary diseases including tuberculosis	–	3
Recurrent ulceration and reoperation	–	2
Pernicious anemia	1	–
Hepatic cirrhosis	–	1
Drowning	–	1
Unknown	1	2

There remained then 295 patients for evaluation of the late results (Tables IX and X). Of these, 58 reported some form of trouble, and were requested to attend the hospital for interview and examination; 52 attended. The examination consisted of careful taking of the anamnesis, general physical examination, blood analysis, including hemoglobin level and red blood cell count, comparison of weight, and investigation of gastric secretion. Unfortunately this last was, for technical reasons, only in the form of Ewald's test meal, and because of the inherent drawbacks of this method the results are given with reservation (Table XI).

TABLE IX. FOLLOW-UP STUDY (295 CASES)

DIAGNOSIS	MEN	WOMEN	TOTAL
Gastric ulcer	50	25	75
Duodenal ulcer	154	66	220
Total	204	91	295

The late disorders following partial gastrectomy were mainly recurrent ulcer of the stomach or duodenum, jejunal ulcer (with Billroth II), gastric hemorrhage without proved ulcer, gastric carcinoma, and intestinal disorders with loss of weight due to nutritional difficulties, including the postcibal complex or dumping syndrome and anemia.

TABLE X. SUMMARY OF RESULTS OF PARTIAL GASTRECTOMY IN GASTRIC AND DUODENAL ULCERS (295 CASES)

YEAR	GASTRIC ULCER				DUODENAL ULCER			
	SYMPTOM FREE	DISORDERS	TOTAL	RECURRENCE	SYMPTOM FREE	DISORDERS	TOTAL	RECURRENCE
1932	5	1	6		6		6	
1933	7		7		10	1	11	
1934	2	4	6		8	1	9	
1935	2		2	1	9	4	13	1
1936	7	2	9		17	3	20	1
1937	5	3	8		15	3	18	3
1938	4		4		9	3	12	
1939		1	1		4	3	7	
1940	3		3		3		3	
1941					1		1	
1942	1		1		4		4	
1943	1		1		7		7	
1944					2	1	3	1
1945	5		5		9	1	10	1
1946	4	2	6		13	5	18	1
1947	2	2	4		7	6	13	
1948	8		8		19	4	23	
1949	4		4		34	8	42	4
Total	60	15	75	1	177	43	220	12

TABLE XI. INCIDENCE OF POSTOPERATIVE FREE HCL AFTER EWALD'S TEST MEAL

DIAGNOSIS	NUMBER OF CASES WITH FREE HCl			TOTAL
	<10	10 TO 19	>19	
Gastric ulcer	21	0	0	21
Duodenal ulcer	24	1	2	27
Total	45	1	2	48

In the present series there were 13 cases of proved or suspected recurrent ulceration (1 gastric and 12 duodenal). Short excerpts from the records of these patients follow:

CASE 1 (No. 130/35).—A man, aged 44 years, with a seven-year history of ulcer treated at home with several periods of dietary management, entered the hospital in 1935. A Billroth I operation was performed, and an ulcer 1 cm. in diameter was found in the lesser curvature. The patient was symptom free until 1942, when there was a slight return of gastric disturbances. Intensification of the ulcer pain with vomiting and food intolerances led to his readmission to the hospital where a diagnosis of ulcer of the lesser curvature was made. Dietary management was instituted and the ulcer healed. Since then the patient has been completely free from symptoms.

CASE 2 (No. 897/35).—A man, aged 41 years, with a four-year history of ulcer treated with periods of hospital management, was admitted to the hospital with hematemesis in 1935. He was treated with medical management followed by a Billroth I operation; kissing ulcers were found in the duodenum. The patient was not helped by the operation. In 1940 he underwent a Billroth II operation at another hospital for recurrent duodenal ulcer. The patient was symptom free until Christmas, 1950, when there was a return of symptoms. He was admitted to the hospital elsewhere with a major hematemesis. X-ray films showed a large jejunal ulcer at the site of anastomosis. Histamine injection revealed gastric secretion with free HCl 25 units. Dietary management was instituted and the patient recovered.

CASE 3 (No. 464/36).—A 51-year-old man with eighteen years' history of recurring ulcer symptoms underwent a Billroth I operation in 1936. The patient was symptom free and had full employment until 1947 when his ulcer pains returned. An x-ray film on

March 13, 1947, showed no definite signs of recurrent ulcer; another on May 27 showed a crater niche, the size of an almond, on the anterior wall of the duodenum. On June 10, 1947, transthoracic vagotomy was performed. Paralytic ileus developed postoperatively and the patient died. Autopsy revealed gross distention of the small and large intestine and recurrent duodenal ulcer.

CASE 4 (No. 1376/37).—A 50-year-old man with a four-year history of ulcer treated with three periods of hospital management underwent a Billroth I operation in 1937. There was a return of symptoms six months later. Ewald's test meal showed free HCl. 48 units and total acidity 66 units. X-ray films showed no definite signs of recurrent ulcer. Following dietary management at home the symptoms subsided. In 1939 there was a recurrence of symptoms. X-ray films now showed a large crater niche in the duodenum. A Billroth II resection was performed; duodenal ulcer was found penetrating to the pancreas and the surface of the liver. The postoperative course was uneventful. Three months later the patient was admitted to the hospital with recurrence of symptoms. X-ray films revealed a large anastomotic ulcer. Ewald's test meal showed free HCl. 55 units and total acidity 74 units. Dietary management was instituted with temporary recovery. Consultation at another hospital showed that the ulcer had increased in size, and on Jan. 19, 1940, a second Billroth II operation was performed. At operation an enormous tumor mass was found on the posterior wall of the anastomosis, with an ulcer the size of a walnut. Following operation the patient's condition rapidly deteriorated and he died on the third postoperative day. Autopsy disclosed degenerative myocarditis; otherwise there was no appreciable disease. There was no evidence of cerebral embolus.

CASE 5 (No. 1412/37).—In 1935 and 1936, a 33-year-old man with an ulcer history from childhood underwent dietary management for duodenal ulcer in the hospital. On June 18, 1937, perforation of the duodenal ulcer occurred; medical treatment was given. Aug. 6, 1937, a Billroth I operation was performed. The patient remained symptom free until 1948 when there was a recurrence. In 1950, he was admitted to another hospital with melena and was later transferred to us. X-ray films showed recurrent duodenal ulcer immediately below the anastomosis. On March 23, 1950, the Billroth I operation was repeated; a large callous ulcer was found on the posterior wall of the duodenum. The patient has experienced a smooth postoperative course, with relief to date.

CASE 6 (No. 917/37).—A 25-year-old woman, with thirteen years' history of ulcer treated repeatedly with hospital management, underwent a Billroth I operation in 1937. A gastric ulcer was found in the lesser curvature and kissing ulcers in the duodenum. The patient remained relatively symptom free until 1941 when she was treated for melena at another hospital. Despite thorough examination, including x-ray, no pathologic changes were seen in the stomach. The patient was discharged, symptom free. She remained well until 1950 when she was again troubled with slight epigastric pain and dyspepsia as well as slight anemia. The patient was admitted to another hospital with uterine hemorrhage where a polyp was diagnosed. Curettage failed to stop the bleeding and subtotal hysterectomy was performed. X-ray examination and inspection of the stomach at the operation showed normal conditions.

CASE 7 (No. 3533/45).—In 1945, a 44-year-old man with several years' history of ulcer was admitted to the hospital with symptoms of gastric retention and underwent a Billroth I operation. Following discharge, he remained well until 1950 when the ulcer symptoms returned. X-ray films showed a suspected recurrent duodenal ulcer. The patient was treated with dietary management and discharged symptom free. In 1951, he was readmitted with intensified symptoms. X-ray films showed a recurrent ulcer in the posterior duodenal wall. On Jan. 13, 1951, he underwent a second Billroth I operation. Since then he has remained symptom free.

CASE 8 (No. 1526/46).—A 22-year-old man with a four-year ulcer history underwent a Billroth I operation in 1946. Kissing ulcers were disclosed in the duodenum. (Three years earlier the patient had had a duodenorraphy for perforated duodenal ulcer.) Slight ulcer

symptoms persisted and the patient was readmitted in 1947. Examination showed a slight gastritis which subsided with dietary management. In 1951 there was a recurrence of symptoms. Examination at another hospital revealed a large calloused ulcer immediately above the anastomosis and a Billroth II resection was performed.

CASE 9 (No. 169/46).—A 60-year-old woman with an eight-year ulcer history had had, in 1944, a Billroth I operation for duodenal ulcer at Mora Lasarett, and, in 1945, she experienced a recurrence of symptoms. In 1946 she underwent a Billroth II operation. The patient remained relatively well until 1947 when she again had severe ulcer pain. A presumptive diagnosis of jejunal peptic ulcer was made and a transthoracic vagotomy performed with relief of symptoms. In 1948, there was a recurrence of ulcer symptoms. The gastric secretion showed a high acid response to insulin injection, indicating that the stomach was not sufficiently denervated. A second transthoracic vagotomy was performed and a state of true achylia obtained, followed by healing of the ulcer. The patient remained well until 1951, when the ulcer symptoms returned. X-ray examination revealed a new jejunal peptic ulcer.

CASE 10 (No. 1651/49).—In 1949 a 22-year-old man, with a four-year history of duodenal ulcer treated with two periods of hospital management, underwent a Billroth I operation. Six months later there was a return of slight gastric symptoms. X-ray pictures showed changes suggestive of a crater niche high on the lesser curvature. The patient was put on a diet in his home and after three weeks reported relief of symptoms. X-ray pictures showed normal conditions.

CASE 11 (No. 2172/49).—On July 28, 1949, a 23-year-old man, with an eight-year history of ulcer treated with two periods of dietary management, underwent a Billroth I operation. The patient remained symptom free for two months, at which time there was a recurrence. He was readmitted to the hospital six months after the first operation. X-ray films showed recurrent ulcer. Gastric secretion showed free HCl. 10 units and total acidity 30 units. Dec. 12, 1949, the patient underwent a second Billroth I operation; a large penetrating ulcer was found on the posterior wall of the stomach. The patient has since remained completely free from symptoms.

CASE 12 (No. 2566/49).—On Sept. 13, 1949, a 65-year-old man with a two-year ulcer history underwent a Billroth I operation for a grossly deformed bulb. The patient remained well until the end of 1950 when the ulcer symptoms returned. X-ray films showed a recurrent duodenal ulcer. Feb. 13, 1951, a second Billroth I operation was performed. A large ulcer crater was found on the anterior duodenal wall immediately below the anastomosis. Since then the patient has been symptom free.

CASE 13 (No. 2918/49).—On Oct. 11, 1949, following two periods of unsuccessful medical treatment, a 28-year-old man with a two-year ulcer history underwent a Billroth I operation. Shortly after his discharge from the hospital the symptoms returned. X-ray films taken in December revealed a recurrent duodenal ulcer. On Dec. 29, 1949, the Billroth I operation was repeated. The patient has since remained symptom free.

In addition to the information obtained through the return visits for check-up examinations and by the questionnaires, data on those who had died during the observation period were obtained from the relatives. In this way a total of 330 patients were traced for evaluation of the incidence of recurrent ulcer. Proved recurrent ulceration leading to reoperation occurred in 10 patients or 3 per cent. Of the other 3 patients with symptoms of recurrence, 1 had melena and the other 2 questionable recurrent ulcer which responded to brief dietary management, leaving them completely symptom free. Recurrent ulcers developed in 1 (1.1 per cent) of the 91 traced cases of gastric ulcer and in 9

(3.8 per cent) of the 239 cases of duodenal ulcer. If the 2 questionable cases are included, the incidence of recurrence amounts to 4 per cent in the entire series.

Gastric carcinoma developed in 5 cases postoperatively. Various explanations have been given for this complication: erroneous diagnosis of the nature of the initial ulcer, carcinoma developing in the gastric remnant due to chronic postoperative gastritis, carcinomatous degeneration of the unremoved ulcer following a palliative operation. Von Haberer[11] stressed that even the most experienced surgeon cannot rule out carcinoma at the operation or at gross examination of the operative specimen. This can only be done by histopathologic examination. Of the 5 cases in this series, a histologic study was made in only 1 instance, and revealed a benign gastric ulcer. In 2 cases the ulcers, the one in the fundus of the stomach and the other in the lesser curvature, were diagnosed as calloused benign ulcers at the operation. This diagnosis was probably incorrect. In the remaining 2 cases only small scars were found on the anterior duodenal wall at operation and it is improbable that they were malignant; the patients died 3 and 11 years, respectively, after the operation.

The so-called *dumping syndrome* or postcibal complex would seem to be peculiar to the gastrectomies. The phenomenon occurs either immediately or shortly after a meal, and is experienced as distress and a feeling of weakness, faintness, cold sweat, cardiac palpitation and, in rare cases, epigastric pain. These symptoms usually disappear after 10 to 15 minutes, especially if the patient is able to lie down for a short while. They seldom cause invalidism, but cases have been known in which reoperation was necessary (Perman[31]). Most of the symptoms gradually improve as the gastric pouch dilates.

In this series the dumping syndrome occurred in 30 (10.3 per cent) of the 293 patients. Two subjects with no dietary restrictions were likely to experience discomfort from eating too rapidly. In the remaining subjects the symptoms consisted of intolerance to certain foods, usually milk dishes, sweet soups, fruit purée, rich pastries, and fatty foods, particularly when taken in large quantities. In all these patients the symptoms were mild and could quite easily be kept under control by merely taking frequent and small meals and avoiding excesses of all kinds. In earlier reports on the occurrence of these symptoms the subjects had for the most part been submitted to the Billroth II operation. A comparison of the results in those series and in the present series is made in Table XII.

It will be noted from the table that the incidence of dumping after the Billroth I and Billroth II operations would probably be similar if the amount of stomach resected was the same. The good results of the Billroth I operation obtained earlier were probably due to the fact that the resection was not as large as that generally made in the Billroth II operation.

A frequent explanation of the cause of these dumping disorders is the rapid emptying of the gastric remnant after resection and the resultant distention of the jejunum.

TABLE XII. INCIDENCE OF DUMPING SYNDROME COMPARED WITH PUBLISHED REPORTS

MATERIAL	METHOD	NUMBER OF CASES	DUMPING	PER CENT
Bruusgaard	Billroth II	364	56	15.6
Ransom	Billroth II	147	21	14.3
Allen and Welch	Billroth II	129	39	30.0
Present series	Billroth I	293	30	10.3

Emptying of the stomach is slower after the Billroth I operation than after the Billroth II operation due to the gradual return of the normal mechanism of gastric emptying, as demonstrable by x-ray examination. It is not improbable that the gastric remnant is an important factor in the production of these disturbances, the explanation being that dilatation of the stomach leads to stimulation of the sympathetic fibers and the appearance of the symptoms. We found, as Perman[31] previously found, that the smaller the capacity of the gastric remnant the greater the incidence of such symptoms. It is noteworthy that the patients ascribed their disorders to overloading of the stomach. It is common experience that these same disorders occur in individuals with normal stomachs following the rapid eating of a large meal with consequent distention of the stomach.

Hypoglycemic attacks 3 to 4 hours after a meal occurred in only 2 cases and were relieved by food.

The postoperative nutritional state of the patients in this series could only be determined by the body weight curve. The postoperative changes in weight are given in Table XIII.

TABLE XIII. POSTOPERATIVE CHANGES IN WEIGHT (279 CASES)

TOTAL NUMBER OF CASES	WEIGHT POSTOPERATIVELY		
	DECREASED	UNCHANGED	INCREASED
279	39	34	206
Per cent	14	12	74

Compared with other series in which the Billroth II operation was performed (Ransom,[33] Gaviser,[8] Allen and Welch[1]), the present series showed only a very small number of patients who had difficulty in maintaining their normal weight. This is not surprising, since the Billroth I operative procedure exerts a more favorable effect on the intestinal function than the Billroth II (Bohmansson,[2, 3] and others). Postoperative diarrhea was a very uncommon complication in this series.

Anemia was reported by 22 patients in their replies to the questionnaires; the lowest level of hemoglobin was 80 per cent. Fifteen of the 22 were examined postoperatively and in each case only a mild secondary anemia was found, easily corrected by administration of iron preparations. In one patient who died during the observation period (Table X) the cause of death was registered as pernicious anemia. This man had a mild hyperchromic anemia before the gastrectomy but at no time during his stay in the hospital was pernicious anemia diagnosed.

Working capacity according to the statements in the questionnaires was reduced in 24 instances. It was found, however, that only in 7 patients or 2.4 per cent of the series could the disability be attributed to the partial gastrectomy. Thus 97.6 per cent of the patients were capable of full work after the operation.

In order to obtain a general idea of the results achieved by the operation the patients were classified into the following groups:

1. Excellent: Complete freedom from gastric symptoms, unrestricted diet, full working capacity
2. Good: Entirely free from symptoms, full working capacity, but still keeping to a somewhat restricted diet
3. Fair: No evidence of ulcer but still considerably invalidated by late disorders
4. Poor: Proved or suspected recurrent ulcer; unimproved or worse since the operation.

The results are summarized in Table XIV.

TABLE XIV. LATE RESULTS OF PARTIAL GASTRECTOMY FOR GASTRIC AND DUODENAL ULCERS

DIAGNOSIS	NUMBER OF CASES	SATISFACTORY		UNSATISFACTORY	
		EXCELLENT	GOOD	FAIR	POOR
Gastric ulcer	75	59 (78.7%)	15 (20%)	0	1 (1.3%)
		74 (98.7%)		1 (1.3%)	
Duodenal ulcer	220	140 (63.6%)	64 (29.1%)	7 (3.2%)	9 (4.1%)
		204 (92.7%)		16 (7.3%)	
Total	295	199 (67.5%)	79 (26.7%)	7 (2.1%)	10 (3.7%)
		278 (94.2%)		17 (5.8%)	

DISCUSSION

A comparison with earlier reports shows that in regard to primary operative mortality and the incidence of recurrent ulceration there was little difference between the Billroth I and Billroth II operations, as seen by the following representative list:

MATERIAL	NUMBER OF CASES	OPERATIVE MORTALITY (%)	RECURRENT ULCERATION (%)
Perman, 1946[30]	278	5.7	—
Bruusgaard, 1946[5]	364	4.0	1.6
Olovson, 1946[28]	424	6.6	1.2
Nicolaysen, 1947[24]	675	3.6	—
Norrman, 1946[26]	501	6.8	2.0
Ransom, 1947[33]	188	7.9	3.0
Gaviser, 1948[8]	394	3.0	0.8
Crile, 1948[6]	140	2.8	—
Present series	364	2.2	4.0

This would seem to support the impression that the good results of partial gastrectomy for gastroduodenal ulcer depend on the amount of stomach resected rather than on the technique used. The incidence of recurrent ulcer seems to be somewhat higher after the Billroth I than after the Billroth II procedure, especially in duodenal ulcers. It is to be noted, however, that recurrent ulcera-

tion after the Billroth I operation may sometimes be cured by medical treatment alone. Recurrence after the Billroth II operation is usually in the form of a jejunal peptic ulcer and calls for operative intervention entailing a high mortality risk. In a few patients in this series, despite Billroth I for the initial ulcer and later Billroth II for recurrent ulcer, a further recurrence occurred in the form of a jejunal peptic ulcer. In one patient (No. 169/46) recurrent ulceration followed Billroth I, Billroth II, and later also vagotomy, despite the fact that the gastric secretion in response to histamine and insulin injections showed a state of true achylia. This substantiates the opinion of Strömbeck[37] and others that hydrochloric acid is liberated when certain unknown elements in the food come in contact with the fundus glands.

Reports that the Billroth I technique predisposes to a higher incidence of gastric retention than the Billroth II do not agree with our experience in this series. In our opinion this is because from anatomic and physiologic standpoints the Billroth I operation is the ideal treatment for peptic ulcer and also because of the careful control and correction of the pre- and postoperative fluid and electrolytic balance and protein deficiency.

A late complication in the form of the dumping syndrome was reported by earlier authors to occur less frequently after the Billroth I operation than after the Billroth II. In the present series it occurred in only 10.3 per cent of the patients, and in no case resulted in invalidism. It would therefore seem that the reduced capacity of the gastric remnant plays an etiologic part in the production of the syndrome, considering the frequency of its occurrence in this series in which, while performing the Billroth I operation, the amount of stomach resected was equal to that usually removed in the Billroth II.

As earlier emphasized by, among others, Bohmansson[2, 3] and von Haberer,[11] the physiologic and consequently the nutritional late results are better after the Billroth I than after the Billroth II operation. In this series only 14 per cent of the patients failed to regain their normal weight. In other series submitted to the Billroth II operation (Ransom,[33] Gaviser,[8] Allen and Welch[1]) the number who lost weight postoperatively was considerably greater.

The duration of postoperative treatment, as well as the number of primary postoperative complications, was considerably reduced by virtue of improved pre- and postoperative treatment, modern anesthesia, and chemotherapy. Since 1947 we have had no deaths attributable to the operation and pulmonary complications in only 4 out of 97 patients.

The subject of the preferred type of gastrectomy is controversial. On the basis of results obtained in the present series we believe we are justified in saying that the late results of the Billroth I and Billroth II operations for gastric ulcer are essentially similar, even in regard to the incidence of recurrence. The Billroth I gives better late result and would seem to be the preferred treatment on account of the better postoperative nutritional state of the patient. The incidence of recurrent ulceration after the Billroth I operation for duodenal ulcer in this series was somewhat higher than after the Billroth II in earlier series. Although this might be an argument against the method it is pointed

out that recurrent ulceration may sometimes be cured by medical treatment. The results of the Billroth I operation for duodenal ulcer and gastric ulcer are similar in regard to improved postoperative nutrition, and only slightly different in regard to recurrent ulcer, and therefore in this respect also the Billroth I and Billroth II operations are of equal value.

SUMMARY

This paper is based on a study of 364 patients with peptic ulcer (103 gastric and 261 duodenal) submitted to the Billroth I operation at the Falun Lasarett during the years 1932 to 1949 and the Mora Lasarett during the years 1938 to 1945. The operative technique was after the method of Bohmansson.[3] From anatomic and functional viewpoints the technique is physiologically better than the Billroth II and in addition permits a resection that is equally large.

The operative mortality rate for the entire series was 2.2 per cent; for duodenal ulcer 1.2 per cent of 261 cases, and for gastric ulcer 4.9 per cent of 103 cases.

The incidence of recurrent ulceration for the entire series was 4 per cent; for duodenal ulcer 3.7 per cent and for gastric ulcer 1.1 per cent.

A late disorder in the form of the dumping syndrome occurred in 10.1 per cent of the patients. In no instance was there a case of invalidism.

The nutritional state of the patients was very good. Only 14 per cent failed to regain their normal weight.

The results of the investigation form the basis for the authors' opinion that the Billroth I operation is the procedure of choice for gastric ulcer and equal to the Billroth II for duodenal ulcer.

A comparison of the results between earlier reported series submitted to the Billroth II operation and the present series shows that the nutritional state of the patients was better after the Billroth I operation than after the Billroth II.

The late results of partial gastrectomy for peptic ulcer support the earlier impression that the amount of stomach resected is of greater importance than the technique employed. The good initial results in the series are ascribed to the improved operative technique, the pre- and postoperative electrolytic fluid and protein control, modern anesthesia, and chemotherapy. Consequently the duration of the postoperative treatment was reduced by half.

REFERENCES

1. Allen, A. W., and Welch, C. E.: Subtotal Gastrectomy for Duodenal Ulcers, Ann. Surg. **124**: 688, 1946.
2. Bohmansson, G.: Studien über die chirurgische Behandlung von Gastroduodenalgeschwüren mit besonderer Berücksichtigung der Operationsanatomie und der postoperativen Digestionsphysiologie, nebst einem Beitrag zur Frage der chirurgischen Behandlung akuter Ulkusblutungen, Acta chir. scandinav. supp. **60**: 1-258, 1926.
3. Bohmansson, G.: On the Technique of Partial Gastrectomy (Billroth I), Acta chir. scandinav. **75**: 221, 1934.
4. Brandberg, R.: Obstruction to Stomach Emptying Following Gastric Resection, Acta chir. scandinav. **100**: 318, 1950.
5. Bruusgaard, C.: The Operative Treatment of Gastric and Duodenal Ulcer, Acta chir. scandinav. (supp. 117) **94**: 1-435, 1946.
6. Crile, G., Jr.: Surgical Treatment of Peptic Ulcer, S. Clin. North America **28**: 1123, 1948.
7. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, J. Physiol. **34**: 133, 1906.

8. Gaviser, D.: Clinical Investigation and Evaluation of Four Hundred Sixteen Cases Consecutively Operated Upon for Peptic Ulcer, SURGERY **24**: 873, 1948.
9. Grevillius, A.: On Complications After Ulcus Resections, Acta chir. scandinav. **100**: 311, 1950.
10. Grevillius, A.: The Surgical Treatment of High-Situated Gastric Ulcers, Acta chir. scandinav. **101**: 283, 1951.
11. Von Haberer, H.: Chirurgische Behandlung des Magen- und Zwölffingerdarmgeschwüres, Zentralbl. f. Chir. **61**: 903, 1934.
12. Hedlund, E.: Den kirurgiska behandlingen av ulcus ventriculi et duodeni, Svenska Läk-Sällsk. Handl. **48**: 167, 1922.
13. Hertel, E.: Experimentelle Untersuchungen über den Einfluss der Magenresektion auf Verdauung im Dünndarm, Arch. f. klin. Chir. **156**: 66, 1930.
14. Higginson, J. F., and Clagett, O. T.: Gastric Resection: Schoemaker-Billroth I Operation, SURGERY **24**: 613, 1948.
15. Hjorth, E.: Postoperative Emptying Difficulties in Direct Connection With Gastric Resection, Acta chir. scandinav. **98**: 385, 1949.
16. Ivy, A. C., Grossman, M. I., and Bachrach, W. H.: Peptic Ulcer, Philadelphia, 1950, The Blakiston Company.
17. Jonsson, S. O.: Spätresultate von Billroth I, Acta chir. scandinav. **78**: 362, 1936.
18. Komarov, S. A.: Studies on Gastrin, Rev. canad. de biol. **1**: 377, 1942.
19. Lahey, F. H., and Marshall, S. F.: Technique of Subtotal Gastrectomy for Ulcer, Surg. Gynec. & Obst. **69**: 498, 1939.
20. Lahey, F. H.: Discussion on article by H. K. Ransom, Ann. Surg. **126**: 653, 1947.
21. Landelius, E.: Radikale Resektion bei der Ulkuskrankheit, Acta chir. scandinav. **82**: 461, 1939.
22. Mann, F. C., and Williamson, C. S.: Experimental Production of Peptic Ulcer, Ann. Surg. **77**: 409, 1923.
23. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**: 265, 1932.
24. Nicolaysen, K.: Mage-och tollfingertarmsårets behandling, Nord. med. **35**: 1533, 1947.
25. Noring, O.: The Effect of Partial Gastrectomy on Gastric Secretion During the Night, Acta chir. scandinav. **100**: 282, 1950.
26. Norrman, E.: Kirurgisk behandling av ulcus, Nord. med. **29**: 409, 1946.
27. Odelberg, A.: Senresultaten av ulcusoperationer, Nord. med. **39**: 1286, 1948.
28. Olovson, T.: Recidiv och postoperativa besvär efter Billroth II, Nord. med. **29**: 404, 1946.
29. Perman, E.: Surgical Treatment of Gastric and Duodenal Ulcer, Acta chir. scandinav. (supp. 38) **77**: 1-333, 1935.
30. Perman, E.: Kirurgiskbehandling av ulcus ventriculi et duodeni, Nord. med. **29**: 373, 1946.
31. Perman, E.: The So-called Dumping Syndrome After Gastrectomy, Acta med. scandinav. (supp. 196), **128**: 361-365, 1947.
32. Pettersson, G.: Ein Beitrag zur Technik und zum Resultat der Methode Billroth I, Acta chir. scandinav. **78**: 335, 1936.
33. Ransom, H. K.: Subtotal Gastrectomy for Gastric Ulcer, Ann. Surg. **126**: 633, 1947.
34. Ringdahl, R.: Prevention of Evacuation Difficulties of the Stomach After Partial Gastrectomy, Acta chir. scandinav. **94**: 397, 1946.
35. Rödén, S.: Postoperative Emptying Difficulties Following Gastric Resections, Acta chir. scandinav. **98**: 99, 1949.
36. Sandberg, I. R.: Postoperative Emptying Difficulties in Direct Connection with Gastric Resection, Acta chir. scandinav. **95**: 286, 1947.
37. Strömbeck, J. P.: Synpunkter på ulkusterapien i belysning av erfarenhet genom sekundäropererade ulkusfall, Nord. med. **29**: 405, 1946.
38. Spath, F.: Studien über die Funktion des reserzierten Magens, Deutsche Ztschr. f. Chir. **233**: 563, 1932; **237**: 128, 1932.
39. Uvnäs, B.: The Part Played by the Pyloric Region in the Cephalic Phase of Gastric Secretion, Acta physiol. scandinav. (supp. 13) **4**: 1-86, 1942.
40. Uvnäs, B.: Antrumslemhinnans betydelse för ventrikelns saltsyresekretion, Nord. med. **46**: 1670, 1951.
41. Velander, E.: Changes in the Cephalic Phase of Secretion Following Gastric Resection in Ulcer, Acta chir. scandinav. **101**: 49, 1951.
42. Wangensteen, O. H., Varco, R. L., Walpole, S., Trach, B., and Hay, L.: Gastric Acidity Before and After Operative Procedure With Special Reference to the Role of the Pylorus and Antrum, Ann. Surg. **112**: 626, 1940.
43. Wangensteen, O. H., and Lannin, B. G.: Criteria of an Acceptable Operation for Ulcer, Arch. Surg. **44**: 489, 1942.
44. Wahren, H.: Discussion, Sv. Kir. Förenings förhandl. **4**: 19, 1945.
45. Wells, C., and Brewer, A. C.: Surgery of Duodenal Ulcer, Brit. J. Surg. **35**: 364, 1948.

LIMITATIONS IN THE CLINICAL USE OF BANTHINE* IN PEPTIC ULCER

Protective Action of Banthine Against the Histamine-Provoked Ulcer in Dogs

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INTRODUCTION

IN THE past two decades, few illnesses have commanded as much attention as peptic ulcer. The volume of literature compiled regarding its etiology and treatment speaks in itself for the complexity of the problem.

With each ensuing year, new medications challenge those already established as aids in ulcer management. Following the revival of vagotomy by Dragstedt,[5] in 1943, renewed interest was manifest in obtaining an anticholinergic medication which would produce a similar blockage of vagus innervation. Years ago, atropine had been used clinically and discarded because of its ineffectiveness in dosages free of undesirable side effects. With Grimson's report,[7] in 1950, of the successful use of Banthine, a new chapter in the medical management of peptic ulcer was opened. Since that time, numerous reports[1, 11-13] have appeared in the literature in agreement with Grimson's earlier findings. Recently its use has been extended to the treatment of herpes zoster,[2] hyperhidrosis,[8] and various disorders of the gastrointestinal tract.[9, 11] One of the most efficacious new applications appears to be the depression of salivation in dental procedures.[4]

From January, 1950, to January, 1952, fifty-two patients were followed while under treatment with Banthine for peptic ulcer. Its inhibiting action on the production of histamine-provoked ulcers in dogs was also studied.

METHOD OF CLINICAL TRIAL

Because of extreme difficulty at times in evaluating changes in deformities alone, a prime prerequisite in the selection of patients for study was the presence of an ulcer crater at the onset of therapy. In only seven instances were cases added in which crater formation was not noted and, in these patients, clinical symptomatology was typical of peptic ulcer and roentgenograms demonstrated definite signs of ulcer activity. Roentgenologic examinations of the stomach and duodenum were routinely obtained immediately preceding the onset of therapy, six weeks later, and then at varying intervals to follow the progress of treatment.

The customary dosages employed at the onset of treatment were 50 mg. fifteen minutes before meals and on retiring for a total of 200 mg. daily. If the

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subjective or roentgenologic response was considered unsatisfactory, the dosage was increased to 50 mg. six times daily or 100 mg. before meals and on retiring. All patients were urged to discontinue other forms of ulcer medication. Dietary restrictions were handled on an individual basis. At most, the patients were placed on a convalescent ulcer diet at the onset of therapy. In instances in which Banthine proved partially or wholly ineffective, either the patients placed themselves on former helpful medications, or stricter ulcer regimens were prescribed by the investigators. Early in the course of therapy, all patients were followed in the outpatient department at weekly or biweekly intervals, and later, if progress was satisfactory, the intervals were lengthened.

Except for patients with intolerable side reactions, the dosage was not reduced until the ulcer was reported inactive on roentgen examination. Then the dosage was gradually reduced to maintenance levels of 200 mg. to 300 mg. daily. With evidence of ulcer recurrence, the dosage was again raised to the level previously necessary to permit healing. Preceding the change to maintenance schedules, all cases had roentgenologically inactive ulcer deformities.

CLINICAL EVALUATION

Between January, 1950, and January, 1952, fifty-two patients with proved peptic ulcer were placed on Banthine. Though admitting that a two-year period of observation is far too short for evaluating the lasting merits of any medication, we believe that sufficient time has elapsed for an appraisal of its limitations.

At the onset of treatment, each patient had symptoms of ulcer activity. There were forty-six individuals with duodenal ulcers, three with gastric ulcers, two with jejunal ulcers, and one with a gastric pouch ulcer after subtotal gastric resection.

Of the fifty-two patients, forty-five had crater formation on roentgen examination at the onset of treatment. Eight patients with ulcer histories of less than one year had ulcers that were considered acute, while forty-four had ulcers that were considered chronic.

Twenty-three patients were regarded as being successfully managed with Banthine, five as being aided, but insufficiently without the help of additional forms of ulcer therapy, and twenty-four as therapeutic failures. Of the twenty-three successful cases, ten have been observed from nineteen to twenty-four months, five from twelve to eighteen months, four from six to eleven months, and four from two to five months. The median duration of therapy was seventeen months. In most instances of Banthine failure, the duration of observation was less than five months. During this period, patients either requested discontinuance of the medication or were considered failures after adequate trial and transferred to the regular gastrointestinal clinic for continued management with an established ulcer regimen. Of the twenty-four failures, fifteen received too little benefit to justify continued use of Banthine as the major form of therapy, five were discontinued because of adverse side reactions, and four developed serious ulcer complications. In all but a few isolated instances, the ultimate failure of the medication, when given alone, could readily be predicted following a trial period of a few weeks.

Range of Dosage.—No definite dosage schedule was suitable in the management of all ulcer patients. Routinely, the investigators have attempted to find the least possible quantity of Banthine necessary to provide healing of the ulcer. Relatively few patients obtained relief from pain or roentgenographic evidence of ulcer inactivity while receiving 50 mg. four times daily. Three hundred milligrams daily benefited a greater number while the most consistent and the most frequent schedule used to obtain satisfactory healing was 100 mg. before meals and on retiring, for a total of 400 mg. daily. In three patients, a total of 500 mg. daily was necessary to obtain a satisfactory result. In many chronic ulcer cases, and occasionally in acute ones, additional antacid medications and dietary restrictions were obligatory to provide satisfactory management. The most favorable results in patients receiving Banthine four times daily were obtained by administering the medication fifteen minutes before meals and on retiring. This is at variance with the six-hour schedule advocated by Grimson.[7] In recent months, 50 mg. of enteric-coated Banthine have been advised in addition to 50 mg. of the uncoated form on retiring, since it appeared that such a combination more readily eliminated the incidence of nocturnal distress. Patients who responded well to Banthine therapy and showed evidence of inactivity on roentgenologic examination were given maintenance dosages of 200 mg. to 300 mg. daily. The authors believe that any maintenance schedule of less than 50 mg. four times daily is of no benefit and that anything less than 100 mg. four times daily will give no assurance against recurrence of ulcer activity. Frequent disagreeable side effects of the medication, however, have precluded the general use of the larger dosage for maintenance purposes.

Of the fifty-two patients, thirty-four demonstrated changes from an active crater to an inactive deformity while on Banthine therapy, though these changes were not always lasting. The daily amount required to obtain this result proved exceedingly varied. Eleven patients changed to inactive deformities while receiving 50 mg. four times daily. Twelve patients, not alleviated by 200 mg. daily, obtained the desired result with 250 mg. to 350 mg. daily, while nine additional patients had healing of the craters with daily amounts of 400 mg. to 500 mg.

These figures are not in themselves significant except for demonstrating the fact that no two individuals can be expected to respond in the same degree to any set regimen of Banthine therapy. For this reason, it would seem best to observe the response while administering smaller dosages before assuming that schedules of 100 mg. four times daily will be necessary for adequate control of individual patients.

Ulcer Recurrence While on Daily Maintenance Dosages.—It soon became apparent that ulcers would recur while maintenance amounts of Banthine were being given. Therefore, all patients in whom healing had been observed on roentgen examination were closely observed through one or more usually troublesome periods of the year. First, roentgen examinations were obtained during usually quiescent seasons to verify the inactivity of the lesion. Then the patients were placed on rigid daily maintenance amounts and instructed not to vary from

the established schedule. They were then seen at frequent intervals, and repeat roentgen studies were performed if clinical symptoms of ulcer developed. Finally, even though they were asymptomatic, gastrointestinal studies were obtained during the period of usual ulcer activity. Of twenty patients evaluated in this manner, thirteen were shown to have developed recurrences. Three patients were being maintained on 250 mg. daily at the time of recurrence of symptoms while ten were receiving 300 mg. to 350 mg. daily during the return of ulcer activity. The daily dosages of patients without recurrent symptoms were similar to those in which a return of ulcer activity was observed.

Ulcer Complications While on Therapy.—Individuals responding well to Banthine therapy cannot be given definite assurance that ulcer complications will not develop while on maintenance dosages. Of thirty-seven patients who initially received definite benefit, four have since had episodes of severe upper gastrointestinal hemorrhage or obstruction of the duodenum. Three instances of upper gastrointestinal hemorrhage requiring numerous blood transfusions, strict Sippy regimen, and hospital admission were observed while the patients were being maintained on 300 mg. of Banthine daily. One patient developed duodenal obstruction while on 100 mg. four times daily. No previous history of obstruction had been observed in this individual and the roentgen examination had initially disclosed complete healing of the duodenal ulcer with 250 mg. of Banthine daily. This patient responded satisfactorily to a strict Sippy regimen and, when the obstruction relented, an active duodenal ulcer with crater formation was noted on roentgen examination.

Adverse Side Reactions.—Table I lists the frequency of adverse side reactions during Banthine administration. Sixty-six per cent of patients observed side reactions of varying degrees, but usually none of these symptoms, except depression of salivation, were troublesome in dosage schedules totaling less than 300 mg. daily.

TABLE I. ADVERSE SIDE REACTIONS FROM THE ORAL ADMINISTRATION OF BANTHINE

	PATIENTS	PER CENT
Excessive dryness of the mouth	28	54
Slowness of urination	10	19
Heartburn following ingestion of Banthine	7	13
Blurred vision	4	8
Constipation	3	6
Conjunctivitis secondary to decreased lacrimation	2	4
Loss of libido	2	4

In three cases, idiosyncrasies in the response to Banthine were observed. In one, crampy abdominal pain and diarrhea were associated consistently with the ingestion of any quantity of the medication. This difficulty disappeared with omission of Banthine and reappeared soon after additional use. The second patient developed a macular papular rash associated with mild pruritus four days after the onset of therapy. No similar dermatologic abnormality had previously been observed and this episode was terminated with the discontinuance of this sole medication. The third patient repeatedly noted the ap-

pearance of marked lassitude, anorexia, and coryza associated with the use of Banthine. Each time, these symptoms were eliminated with the discontinuance of the medication.

PROTECTIVE ACTION OF BANTHINE AGAINST THE HISTAMINE-PROVOKED ULCER IN DOGS

In the past these laboratories have found the use of chronic histamine stimulation in dogs a reliable means of measuring procedures adopted clinically to treat peptic ulcer. Lannin and associates,[10] using histamine-in-beeswax stimulation, were able routinely to produce jejunal ulceration in dogs subjected to either gastrojejunostomy or small gastric resection, but noted that 75 per cent gastric resection fully prevented stomal ulceration. Fast[6] likewise noted the Sippy regimen to be effective in preventing histamine-provoked ulceration in dogs. A close correlation between these experimental results and reports in the literature, using similar modes of ulcer therapy in man, have frequently been observed. To further evaluate Banthine as a medication effective in combating the ulcer diathesis, experimental studies were undertaken concomitantly with the clinical evaluation.

Laboratory studies were carried out on twenty-eight adult mongrel dogs ranging in weight from 16 to 34 pounds. Histamine-in-beeswax was prepared after the method of Code and Varco.[3] Banthine-in-beeswax was prepared in a similar manner. At 4 P.M. daily, 75 mg. of Banthine were injected into thirteen dogs while 37.5 mg. were given to fifteen others. In addition, each animal received, in a separate site, an injection of 30 mg. of histamine base. Following the injections, the feed pans were removed and no food was offered until the following morning. The dogs were then given routine kibbled dog chow with an added supplement of horse meat. If the animals did not succumb from an ulcer produced by the histamine implantation, they were sacrificed after the completion of the forty-five day period. In order to establish the potency of each batch of histamine-in-beeswax, random samples of each supply were given daily to control dogs and routinely produced gastric or duodenal ulcerations. To provide evidence for the elimination of Banthine as an agent responsible for mucosal ulceration, two groups of two animals were daily injected with 75 mg. or 37.5 mg. of Banthine-in-beeswax over a forty-five day period and in no instance was ulceration found on necropsy.

Of the twenty-eight dogs used in the study, three developed duodenal or gastric ulcerations. One dog, receiving 37.5 mg. of Banthine daily, died after forty-three injections and was found to have a typical sealed off antral perforated ulcer. Two animals which died of distemper had mucosal ulcerations of the duodenum. Of the remaining twenty-five dogs, twelve survived the forty-five day period of injections of histamine-in-beeswax and Banthine-in-beeswax and were found, at necropsy, to have entirely normal gastrointestinal tracts. Thirteen animals died due to distemper before completion of the forty-five day injection period and were also observed to have no evidence of peptic ulceration.

DISCUSSION

Though undoubtedly an important addition in the treatment of the ulcer patient, a less enthusiastic outlook must be realized than has been expressed

by most authors up to the present time. Fully recognizing the small number of clinical cases and the short length of time involved in our study, the authors feel able at least to point out the inadequacies of this medication in a considerable percentage of ulcer patients. Banthine has proved to be insufficient as the sole form of therapy in the majority of cases, though definitely an aid when utilized in combination with other forms of ulcer management. Unfortunately, the larger, more effective dosage schedules are accompanied by a moderately high frequency of annoying side reactions which nullify, somewhat, the advantages of the increased effectiveness. The antispasmodic action of this agent is quite evident clinically, but this feature greatly increases the difficulty of subjectively determining the degree of ulcer activity. It is far from uncommon to find, on roentgen examination, an active ulcer with crater formation in patients who are, for the most part, subjectively free of all distress. Therefore, we have concluded that only fluoroscopic examination and roentgenograms can be relied upon as guides to the effectiveness of the treatment. Because of the recurrence of ulcer activity, in the majority of cases, on rather large maintenance dosages (200 mg. to 350 mg. daily) and the appearance of serious ulcer complications in four instances, it is felt that no definite long-term assurances can be given these patients even with initial healing of the ulcer crater. It would seem from our observations that except in mild cases, Banthine should be used only in conjunction with other time-honored forms of peptic ulcer management.

Findings somewhat different were noted in the experimental studies, for the laboratory results indicate that Banthine is very effective in protecting gastric and duodenal mucosa from ulceration produced by chronic histamine stimulation. The discrepancy between the experimental and clinical results, however, may be due to the slower and more complete absorption of Banthine when given parenterally in animals as compared to the more rapid and more erratic absorption when taken orally by man.

SUMMARY

1. Fifty-two patients with peptic ulcer were followed for varying periods of time from January, 1950, to January, 1952.

2. Twenty-three cases were considered successfully managed with Banthine, five aided by the medication, and twenty-four therapeutic failures.

3. Sixty-five per cent of the series, at some period of time during Banthine therapy, demonstrated a change on roentgen examination from an active crater to a deformity with no evidence of activity.

4. The most effective dosage schedule of Banthine found was 100 mg. four times daily.

5. Adverse side reactions occurred in 66 per cent of the patients studied.

6. Four instances of severe upper gastrointestinal hemorrhage or obstruction occurred while on maintenance dosages of Banthine.

7. Twelve of thirteen dogs were protected by Banthine from histamine-provoked ulcer.

REFERENCES

1. Brown, C. H., and Collins, E. N.: The Use of Banthine in the Treatment of Duodenal Ulcer: Preliminary Report on Its Use in 137 Patients, Gastroenterology **18:** 26-35, 1951.
2. Brown, H. S., and Riekie, R. D.: Banthine in Herpes Zoster, Northwest Med. **50:** 432, 1951.
3. Code, C. F., and Varco, R. D.: Chronic Histamine Action, Proc. Soc. Exper. Biol. & Med. **44:** 475-477, 1940.
4. De Bré, A. J.: A Clinical Report of 100 Cases Using Banthine as an Antisalogogue in Dental Procedures, Dental Digest **57:** 210-211, 1951.
5. Dragstedt, L. R., and Owens, F. M., Jr.: Supra-Diaphragmatic Section of the Vagus Nerves in Treatment of Duodenal Ulcer, Proc. Soc. Exper. Biol. & Med. **53:** 152-154, 1943.
6. Fast, J., Friesen, S., and Wangensteen, O. H.: The Sippy Regimen Protects Against the Histamine Provoked Ulcer, Gastroenterology **8:** 662-664, 1947.
7. Grimson, K. S., Lyons, C. K., and Reeves, E. J.: Clinical Trial of Banthine in 100 Patients With Peptic Ulcer, J. A. M. A. **143:** 873-877, 1950.
8. Grimson, K. S., Lyons, C. K., Wetkins, W. T., and Callaway, J. L.: Successful Treatment of Hyperhidrosis Using Banthine, J. A. M. A. **143:** 1331-1332, 1950.
9. Kern, F., Jr., Almy, T. P., and Stolk, N. J.: An Experimental and Preliminary Clinical Study of the Effect of a New Quaternary Amine, Banthine, Upon the Human Colon, Gastroenterology **17:** 198-208, 1951.
10. Lannin, B. J., Hay, L. J., Judd, E. S., and Wangensteen, O. H.: Evaluation of a Satisfactory Operation for Ulcer, Proc. Soc. Exper. Biol. & Med. **56:** 231-233, 1944.
11. McDonough, F. E., and O'Neil, P. B.: The Therapeutic Value of Banthine in Gastrointestinal Disorders, Gastroenterology **19:** 265-282, 1951.
12. McHardy, G., Browne, D. C., Edward, E., Mareck, F., and Ward, S.: An Evaluation of Banthine in Ulcer Management, New Orleans M. & S. J. **103:** 380-386, 1951.
13. Winkelstein, A.: Banthine in the Therapy of Peptic Ulcer, J. A. M. A. **144:** 1501-1502, 1950.

SOME ASPECTS OF "SENILE" GANGRENE

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THE choice in the title of an obsolescent adjective to define a type of gangrene was made for two reasons. The first is a plan to review some of what may be called the more senile concepts of arteriosclerotic gangrene and the second is that this discussion will be concerned largely with gangrene in the older age groups. During the last fruitful twenty years or more the emphasis on study of and practice in all types of peripheral vascular disease has been on the prophylaxis of gangrene by hygienic treatment and by sympathectomy. When gangrene is established there is a growing—and an admirable—tendency toward the conservation of tissue. The reasons for this latter development will be discussed and the propriety of its application in gangrene in the old will be questioned. It is temerarious to discuss this topic before the Texas Surgical Society, among whose members there are so many who have done important investigative work on the peripheral vascular diseases.

In reviewing the older literature it is interesting to observe the growth of interest in peripheral vascular disease—a growth at least partially due to the increasing age of the population and one that is familiar to all. A most striking instance is afforded by the textbook of surgery used in Harvard Medical School in 1913 and 1914, namely, Mumford's *Practice of Surgery*,[1] the date of which is 1910. This book contains no index reference to gangrene of the extremities. In a long chapter on amputations, concerned largely with acute trauma, there is only a passing reference to gangrene as an indication for amputation. In medical school teaching of those years, there were presented only two major types of gangrene resulting from generalized vascular disease, namely, juvenile (or presenile) and senile gangrene, which were distinguished only by the age at which they appeared. A few specific etiologies were referred to, such as diabetes and syphilis. It was recognized that certainly the great majority of cases of senile gangrene were the result of arteriosclerosis. In 1908 Buerger,[2] following von Winiwarter, separated from the hitherto unidentified gangrenes of young people an underlying disease with a specific pathology and a characteristic clinical course which he named thromboangiitis obliterans. It may be wondered, now that the prevention of gangrene in this disease is frequently accomplished by prophylactic measures so that pathologic study of the vessels is not too frequent, whether there are entities in this "juvenile" group which have still not been recognized; in other words, whether we are using the term "thromboangiitis obliterans" to define all gangrene in the young in a self-satisfied way which is almost as concealing of our ignorance as our earlier use of the term "juvenile gangrene." Although this may be improbable,

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it seems stimulating to make a mental reservation in diagnosing thromboangiitis obliterans in those cases not confirmed by pathologic study. There is still a challenge in gangrene in the young.

During the growth of knowledge of peripheral vascular diseases the major emphasis, particularly in recent years, has been on the vasomotor aspects of the major and collateral circulation. Investigations of sympathetic nerve function in connection with the peripheral vascular diseases have led to a large increase in our understanding of them and a great addition to our capacity to protect the patient from the onset of gangrene and to limit gangrene if it has occurred.

One of the most significant recent increases in understanding is the concept that we cannot regard an extremity as a single unit, insofar as its blood supply is concerned. In the early days of the study of ischemia, an extremity was considered to have either enough blood supply to survive as a whole or so little that it would die as a whole. This, of course, is still within limitations a logical concept when there is acute mechanical blockage of major arteries. It is not a logical concept as applied to the irregular and incomplete blockages of peripheral vascular disease, especially when modified by the presence of vasospasm.

One must now think of the musculoskeletal system separately from the integument. The former has the function of locomotion and heat production and the latter the function among others of heat regulation. One might therefore expect a priori that the two major elements of an extremity would react differently to sympathetic stimuli or interruption of the sympathetic impulses. This has been found by careful studies to be the case.[3-5] These observations may help to explain the lack of correlation now so well recognized between the skin temperatures and the relief of symptoms following sympathetic interruption. One no longer judges the propriety of sympathetic ganglionectomy entirely by preoperative observations of the skin temperature after block of the sympathetic nerves. This is an important new concept that may lead to further improvements in our treatment of peripheral vascular diseases.

However, in this presentation there will be no further discussion of the vasomotor aspects of peripheral vascular disease, because they are the foremost phase of present-day interest and therefore can be assumed to be in the daily thought of all. As said earlier, arteriosclerotic gangrene is the subject of this talk and nothing further will be said about other aspects of vascular disease. It should be understood clearly that what is said will not apply to thromboangiitis obliterans nor to infection (or even gangrene) in those diabetics in whom the factor of ischemia is relatively minor.

Let us now turn to some of the underlying principles that determine the establishment of gangrene. The fundamental cause of death of tissue from lack of oxygen is not an equation that can be quantitatively expressed in absolute terms, nor one that remains constant in any single case. It is a relative matter which involves many variables. Death of tissue occurs when there is a critical negative disproportion between available oxygen and the needs of the tissue at any particular time. Since necrosis is an irreversible process, the necessity to provent this disproportion from reaching the critical level even for a few minutes is the general basis for the prophylaxis of gangrene.

From the point of view of the supply of oxygen one must consider not only the mechanical factor of the total cross section of the arterial supply, including the collaterals, but also a complex array of other factors. These include cardiac output, the presence or absence of anemia, and the effect of gravity. (Nowadays one rarely sees the ischemic extremity propped on a pillow.) In addition they include the effects of vasospasm whether it be produced by the arterial disease itself or by environmental factors such as general or local chilling. We have all seen the onset of gangrene in an individual who sleeps a drunken night in the cold air, the temperature of which may be well above the level at which frostbite can be expected.

The needs of the tissue for oxygen are increased above the basic resting requirements by three main factors, each of which determines a local increase in the rate of metabolism and hence in oxygen thirst. The first of these is activity, which we regularly recognize by putting the ischemic extremity at rest. This factor will be discussed later. The second is the increase in metabolism which occurs with local warming of the part. It is only fairly recently that we have recognized the importance of this deleterious influence. The old days of hot soaks and of heat cradles are fortunately over. The third factor is not so often a part of common thinking about tissue necrosis. Nevertheless, it is equally important, particularly in connection with the choice of the level for amputation. It consists of an increase in metabolism demanded by the initiation of the inflammatory process as the result of necrosis, of infection, or of trauma. These local metabolic considerations adequately explain such occurrences as the onset of gangrene after a day's hunting and the spreading necrosis supervening upon infection in the ischemic limb. Much more important for our purpose today, they explain also the spread of gangrene that may occur after amputation at a level that from the local circulatory aspect is judged to be safe. It must be re-emphasized that even a temporary disproportion between availability of oxygen and increased demand will precipitate a process from which affected tissue cells will not recover.

Perhaps the idea can be more clearly expressed if we now consider briefly the significance of the line of demarcation. If a toe with normal blood volume flow is devitalized by crushing, there is an immediate inflammatory response to the dead tissue which has become a foreign body. The process of necrosis spreads no further. In the ischemic foot, however, whatever may precipitate the gangrene, the attempt to set up a corresponding inflammatory response, resulting in a demand for more oxygen, may create the critical disproportion under discussion. The outcome may be necrosis in previously undamaged and apparently viable tissue. The gangrene will advance proximally until it reaches a level where there is enough blood to support the inflammatory reaction which is needed to limit the process.

The important thing to remember is that at the time a line of demarcation forms, the tissues just below the line of demarcation have had just enough deficit of oxygen to die, whereas the tissues immediately above the line of demarcation have had just enough oxygen to survive and to nourish inflammation. Although

the skin may be warm and may present obvious capillary circulation, yet it may very well not have a large enough blood supply to support the additional need created by inflammation resulting from an added load of trauma. This explains the frequent observation that an incision even some inches above a line of demarcation may be followed by progressive necrosis of skin and deeper tissues, which will proceed proximally until the balance between need and availability is again established and a new line of demarcation forms. We have all seen this phenomenon occur even when the level of amputation has seemed more than adequately high in relation to the line of demarcation.

In speaking of the line of demarcation one must remember an important additional consideration that may be related to the differences in function between the skin and the deeper tissues already referred to. More often it is probably due to chance variations in arterial occlusion. The older observers, following the concept of the arterial function of the extremity as a unit, often thought of the line of demarcation as running in the deep tissues as a plane from its superficially obvious border on one side of the extremity to its border on the opposite side. This is no longer a tenable conception. Gangrene may occur with the line of demarcation in the skin running irregularly about the ankle and the line of demarcation of the calf muscles at their superior attachments to the femur. Conversely, gangrene at the tip of a digit is not uncommonly limited to the skin alone with preservation of the viability of deeper tissues.

Uncertainty as to the availability of oxygen under conditions of increased need created by the trauma of incision together with the variable topography of the line of demarcation bedevils the surgeon in his choice of the level for amputation. Unfortunately there is not available for routine clinical use any methods that will tell him either what punishment the circulation of the skin will take in the form of additional trauma or how close to the border line the deeper tissues are. Unfortunately such tests of skin circulation as the saline wheal and the histamine flare, although sometimes useful, cannot be quantitated against the demands for oxygen caused by traumatic insult, nor can the older tests of reactive hyperemia such as those of Moschkowitz and Matas. If these tests show markedly diminished circulation we may have a warning, but we have no assurance that, where the reaction seems adequate, incision will be safe. As for the deeper tissues, the uptake of radioactive sodium injected into muscle has proved a useful laboratory method of study. It, however, is not available for routine clinical use and, furthermore, it has not been calibrated against the incidence of progressive necrosis following the trauma of amputation.[6]

The next aspect of the problem to be discussed is the gross pattern of arterial occlusion in arteriosclerosis as related to the normal anatomy. In a series of pathologic and radiographic studies of the arteriosclerotic arterial trunks in amputated gangrenous extremities carried out many years ago,[7] it was observed that many legs showed the most marked vascular narrowing at the bifurcation of the popliteal artery, where also the greatest number of complete occlusions

occurred. It is interesting to speculate on a possible explanation for this localization of the most advanced stages of the disease. The thrust of the pulse in the normal artery is both lateral and longitudinal (Fig. 1). When the arterial wall loses its elasticity, little of the thrust can be absorbed laterally and its force is largely directed in the longitudinal axis of the vessel. You will remember that the popliteal bifurcation rides astride the upper border of the interosseous membrane of the lower leg, a border of a sharp and unyielding character. One can presume that the longitudinal thrust of the pulse of the inelastic vessel subjects the distal angle of the bifurcation to rhythmic repeated minor trauma. In any event there is evidence that this site is one of the common sites for arterial occlusion in arteriosclerosis, often supplemented, of course, by the occurrence of thrombosis upward and downward. It is true that not all occlusions occur at this point, but this locus of occlusion is frequent enough to influence our thoughts about collateral circulation. It is parenthetically interesting that Buerger[2] also named the bifurcation of the popliteal artery as among the more common sites of occlusion in thromboangiitis obliterans.

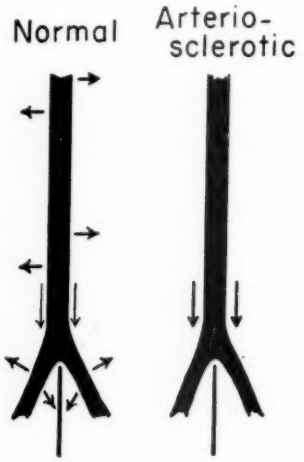


Fig. 1.—Possible mechanism of localization of most advanced stage of arterial disease at the bifurcation of the popliteal artery. In arteriosclerosis most of the thrust of the pulse is longitudinal, driving the bifurcation down upon the sharp edge of the interosseous membrane.

The anatomy of the collateral vascular supply to the lower leg constitutes such an important part of the argument that perhaps one may be pardoned for reviewing it here. We all know how frequent the occurrence of gangrene is after ligation of the healthy popliteal artery, an occurrence explainable on the basis of available collateral channels (Fig. 2). In the first place the terminal branch of the profunda femoris does not anastomose with arteries about the knee, and is therefore not a potential collateral pathway. On the other hand, the descending branch of the lateral circumflex iliac and the highest genicular from the superficial femoral terminate as fine vessels in the anastomotic complex about the knee joint anteriorly. These are the only arteries arising above the superior border of the popliteal space to furnish collateral to the popliteal artery. There are two pairs of arteries that arise from the popliteal artery just

above and below the knee, the lateral and medial genicular arteries, superior and inferior, respectively. These four vessels anastomose through the fine reticular network already mentioned in the superficial tissues about the knee anteriorly. In addition there is a single branch of moderate size which arises from the anterior tibial artery after it passes anterior to the interosseous membrane, known as the anterior tibial recurrent, which also joins the anastomotic network of vessels. The middle genicular artery, arising between the condyles of the femur, is largely distributed to the ligaments and synovial membranes in the interior of the articulation of the knee and takes little part in collateral supply. The important point is that the total caliber of the vessels feeding the network about the knee from above is less than the caliber of the popliteal artery. This disproportion explains the risk of gangrene after acute ligation of the undiseased vessel.

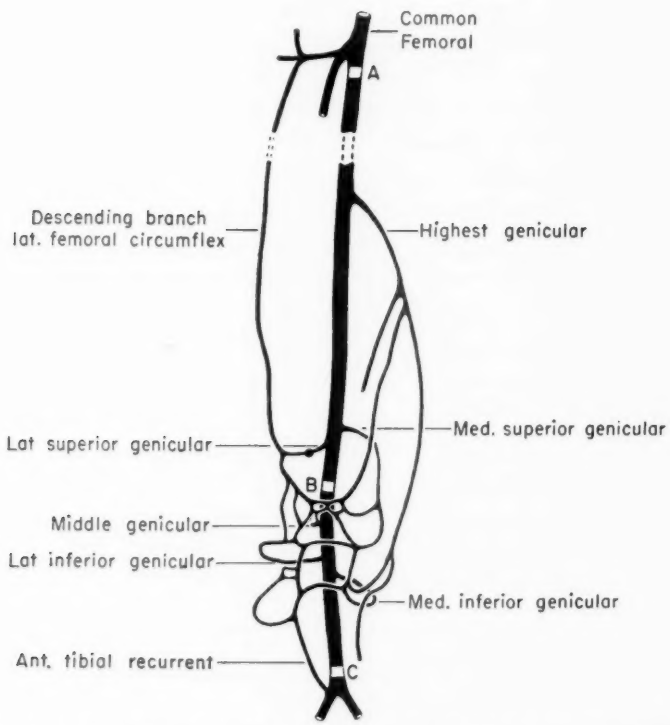


Fig. 2.—Diagram of collateral circulation about the knee joint. If occlusion occurs at *A* the tissues of the thigh receive adequate blood from the deep femoral artery, whereas all collateral for tissues below the knee must be carried by the descending branch of the circumflex iliac. At *B* there are available also the highest genicular and the two superior genicular arteries to feed through the superficial net of fine vessels anterior to the joint. In obstruction at *C* the only route of collateral is through the recurrent tibial artery.

Since most often the final complete occlusion of a major vessel such as the popliteal artery in arteriosclerosis is thrombotic or embolic in origin and therefore relatively abrupt in occurrence, the situation seems to resemble that existing when the healthy artery is suddenly occluded. Slowly progressive narrowing of the major vessels in arteriosclerosis does not seem often to stimulate enlargement of the cross section of available collateral. One can rarely if ever

detect by palpation about the knee joint in this disease the superior and inferior genicular vessels which are often readily felt when aneurysm or arteriovenous fistula involves the popliteal artery.

Whether the top level of total occlusion of the blood supply to the leg is at the bifurcation of the popliteal or whether it is in the popliteal space, or whether, in fact, it is in the superficial femoral, the effect on circulation below the knee joint can on anatomic grounds be approximately the same, as illustrated in the diagram (Fig. 2). There are differences in available collaterals, but on the whole the blood supply to the lower leg and foot is necessarily markedly diminished. The deep femoral artery is infrequently occluded by arteriosclerosis except when high thrombosis of the superficial femoral occurs. Hence, although the tissues above the knee will sometimes not stand amputation and will be the site of spreading gangrene, yet this occurrence is relatively infrequent. A functioning deep femoral artery will support all tissues above the knee; if gangrene occurs following an above-knee amputation, the assumption is that there is a high level of thrombosis. In such cases there is clearly no question of choice of the level of amputation as regards a site above or below the knee.

Many of these considerations lend support to the traditional practice in arteriosclerotic gangrene of amputation no lower than the knee. When minor degrees of necrosis exist, such as gangrene limited to a part or all of one or two digits, spontaneous amputation aided by débridement through the line of demarcation and not above it, so as to avoid summoning a new inflammatory process in the spared tissue, has been the second element in standard practice. In recent years the trend toward the conservation of tissue in arteriosclerotic vascular disease has been initiated. There are sound reasons for this trend. Shumacker and Moore have recently reported their experience with amputations below the knee and have summarized the problem succinctly and, with one exception, completely.[8] It is the single omission in their discussion on which most weight will be placed in this discussion.

Although in all conditions one is desirous of avoiding the sacrifice of living tissue, the reasons for the swing toward conservation of tissue in gangrene are of two varieties. In the first place, the steady drop in the mortality rate for amputation, which parallels or even perhaps exceeds the drop in the mortality rate for all surgical operations, has relieved the surgeon of some of his dread of the possible necessity for a higher amputation if necrosis supervenes in the stump following a lower leg or foot amputation. The drop in the mortality rate is due to a number of factors including improved anesthetic methods and increased ability to control infection through the use of antibiotics. Another important element in the reduction in mortality, often cited, is the opportunity to prepare the patient at leisure for definitive amputation by what has been called physiologic amputation by the tourniquet with preservation of the physiologically detached extremity by reducing its temperature. Whether or not the procedure of refrigeration is or is not a useful means of reducing mortality will be briefly discussed later. Among improvements in anesthesia we do not include refrigeration anesthesia; in refrigerated cases we have been careful that the amputation be carried out in tissue which has not been chilled.

The second reason for the modern trend toward conservation of tissue is the belief that the danger of postamputation spreading necrosis has been diminished. There is reliance, often justified, on the effectiveness of sympathectomy in so successfully increasing the caliber of collateral vessels as to permit the sparing of the knee joint. Furthermore, there seems to be an impression that the estimation of circulatory capacity is more accurate than in the past. This impression, as indicated earlier, can be doubted. The results of oscillometry and of arteriography seem to bear only a limited relationship to the safe level of amputation. Only the time-honored method of incision into the skin and muscles below the knee to observe the amount of bleeding that occurs has been widely accepted as a useful guide. Even with this highly subjective method, the effect of trauma on oxygen demand remains an unpredictable factor. Perhaps it is pessimistic to conclude that modern study of the patient with arteriosclerotic gangrene has added little to help guide the surgeon in the important decision. One can hope that further study and application of the uptake of radioactive sodium may offer clinical promise at some future time.

Amputation at any level in arteriosclerotic gangrene is safer than it was fifteen years ago and the results of lower leg amputation in this disease have been reported to compare favorably with more radical amputation under present conditions.[8] The experience at the university of Virginia Hospital is almost entirely confined to amputation above the knee, a procedure to which we have persistently clung. It is reported here, not because it supports the main argument, but because it indicates a correlation between the mortality rate of major amputation and the nature of the clinical material presented. Such correlation suggests caution in applying the published reports of one clinic to the problems of another.

TABLE I. AMPUTATION MATERIAL, UNIVERSITY OF VIRGINIA HOSPITAL, 1947 TO 1951 INCLUSIVE

	NUMBER	MEAN AGE
Arteriosclerosis	48	72.8 years
Arteriosclerosis with diabetes	27	65.4 years
Total	75	70.1 years
Transmetatarsal, 1——Supracondylar, 74		
Men, 50——Women, 25		
White, 46——Negro, 29		

In the five years, 1947 to 1951 inclusive, seventy-five amputations have been performed in the University of Virginia Hospital for arteriosclerotic gangrene (Table I). Of these only one was below the knee, a transmetatarsal procedure requiring reamputation above the knee. Our patients are largely rural and often neglected medically, especially in the case of the Negroes. The type of problem encountered is illustrated by the high mean age of our arteriosclerotic patients without diabetes, namely, 72.8 years. This compares with Shumacker and Moore's mean age of 71.4 years in the same group. Our diabetics also average about one and one-half years older than theirs. Such a difference in

mean ages clearly indicates a considerable numerical preponderance of extreme age in the higher series. The five and one-half year differential in mean age (Table II) between the patients who lived and those who died indicates the influence of advanced age on mortality.

TABLE II. MEAN AND EXTREME AGES AS RELATED TO SURVIVAL AND DEATH. AMPUTATION MATERIAL, 1947 TO 1951 INCLUSIVE

	SURVIVED	DIED
Mean age	69.2 years	74.6 years
Maximum age	90.0 years	94.0 years
Minimum age	50.0 years	65.0 years

The bad-risk cases have been estimated by reviewing the histories without knowledge of survival or death (Table III). With one possible exception, the criteria that determined the denomination of a patient as a bad risk would be indisputable; the exception is the inclusion in this category of patients so advanced in senility as to be completely disoriented. As is seen, about 30 per cent of the patients were in the bad-risk category. That judgment in deciding what patients were to be called bad risks was not too inadequate is indicated not only by the fact that two-thirds of those patients who ultimately died were placed in that category as compared with one-fifth of those who survived, but also by the fact that the mortality in the bad-risk cases was three times that in the good-risk cases.

TABLE III. DISTRIBUTION AND MORTALITY OF BAD-RISK CASES*

	NUMBER	MEAN AGE	PER CENT
Survivals	14	72.6 years	22.2 of all living
Dead	8	71.6 years	66.6 of all dying
Total	22	72.3 years	29.3 of total cases
Mortality bad-risk cases, 28.6 per cent Mortality good-risk cases, 9.5 per cent			

*Designation of bad risk was made without knowledge of survival or death.

The gross mortality rate in this series was 16 per cent, a figure not to be compared with the results in recently published series (Table IV). Considering the quality of the material, one need not be too discouraged by this figure. It compares with a mortality rate in unpublished data from this clinic collected about fifteen years ago of between 25 per cent and 30 per cent. When the bad-risk cases are removed from the picture, the mortality rate drops to 5.9 per cent. The year 1947 was a bad one. Five bad-risk cases were admitted and all five died. For the past four years our gross mortality rate was 12.3 per cent. Our mortality rate in 1951 (one death in eighteen cases) was 5.5 per cent.

Without seeking excuses for a relatively poor total mortality record, one may perhaps be justified in the comment as made before, that in a small series the results will depend more upon the quality of the clinical material presented than, within limits, upon the quality of surgical care. In any event, our own improvement has been real and the fact remains that reamputation, after an unsuccessful conservative procedure, is less to be dreaded than it once was.

TABLE IV. GROSS MORTALITY AND MORTALITY AS COMPARED WITH THE PRESENCE OF DIABETES (1947 TO 1951 INCLUSIVE)*

	NUMBER	DEATHS	MORTALITY
Arteriosclerosis	48	9	18.7%
Arteriosclerosis with diabetes	27	3	11.1%
Total	75	12	16.0%

Total cases, 75 less 8 (bad risks dead)	=	67
Total deaths, 12 less 8 (bad risks dead)	=	4
Mortality corrected for bad risk	=	5.9%
1948 to 1951 inclusive—cases, 57; deaths, 7; mortality,		12.3%

*Note that the subtraction of the bad-risk cases reduced the mortality by almost two-thirds. Note also the gross mortality when one bad year is subtracted.

For the record, there is reported the experience with the healing of stumps. Only one reamputation was necessary, namely, in the single case of transmetatarsal amputation already noted. There were twenty-seven of necrosis or infection with a high mortality. Nine of the instances of infection are duplicated in the total of patients developing necrosis. Both infections and necrosis were often minimal. An estimate of delay in healing is always subjective, and in many instances delay results in only slight morbidity. The great majority of the stumps were closed by loose skin approximation, often with the insertion of drains.

TABLE V. HEALING OF STUMPS

	NUMBER OF PATIENTS	
Reamputation	1	(transmetatarsal)
Necrosis (all grades)*	15	(5 dead)
Infection (all grades)	12	(4 dead)
Delay	25	
Delay without infection or necrosis	12	

*The cases of necrosis are duplicated in most instances in the number of cases shown for infection.

The study of this material has uncovered one observation, unrelated to the general theme of this discussion, which may be presented parenthetically. Dr. Minor of the University Hospital surgical staff suggested that the incidence and causes of death in patients prepared for amputation by refrigeration be investigated. His clinical impression had been that deaths in this group were numerous and included a high proportion of embolism as the etiologic mechanism. The results (Table VI) suggest that his impression is correct, at least in this clinic. The mortality of refrigerated cases was over twice that of the overall mortality. That this was not due to the selection for refrigeration of only bad-risk cases is shown by the fact that the latter comprised less than one-half of the refrigerated cases. Furthermore, of seven deaths following refrigeration, four were sudden and unexpected. Unfortunately, in none of these four cases was post-mortem study permitted; death from plmonary embolism is thus only a clinical inference. However, a priori the occurrence of stasis phlebothrombosis above the tourniquet seems a not improbable event. This possible danger of refrigeration has received little or no comment. The parenthesis is presented only to suggest that others study their material to determine whether the implications of the present limited study are supportable.

TABLE VI. CASES PREPARED FOR AMPUTATION BY REFRIGERATION, SHOWING THE PERCENTAGE OF THOSE REFRIGERATED WHICH WERE BAD-RISK CASES AS WELL AS THE MORTALITY OF REFRIGERATED CASES

PREPARED BY REFRIGERATION			
Cases	20	percent of total cases	26.6%
Bad risks	8	percent of total refrigeration	40.0%
Deaths	7	mortality	35.0%
Of 7 deaths, 4 were abrupt and unexpected (embolism?)			

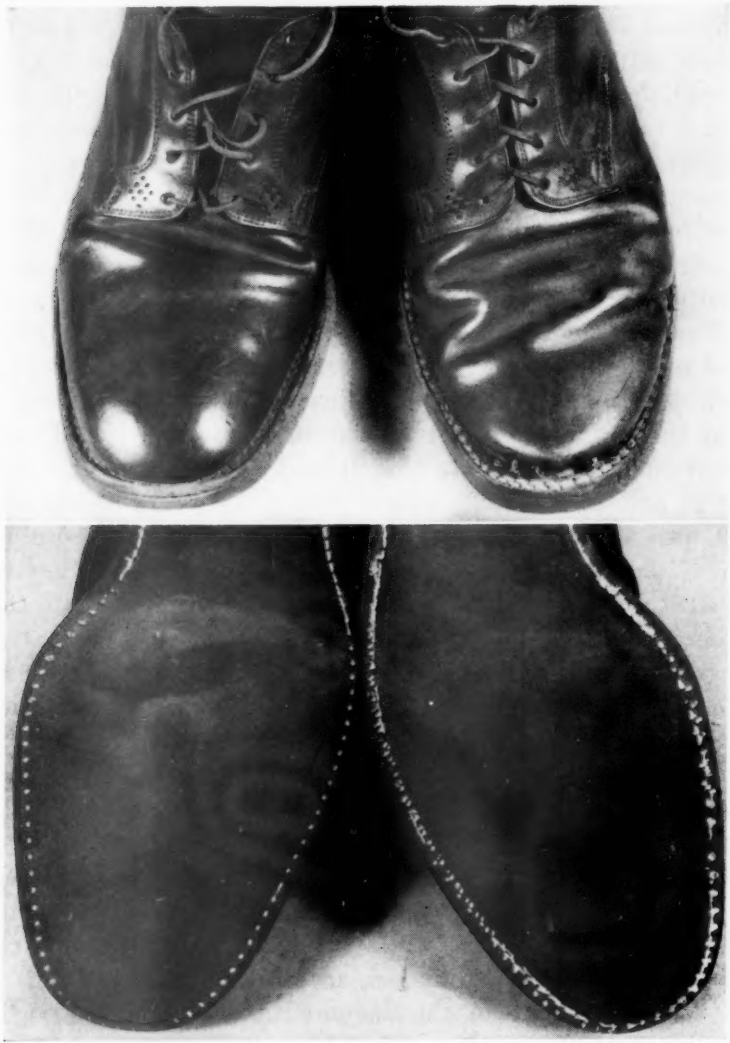
The basic motivation of the trend toward saving tissue is of course the desire to rehabilitate the patient to as nearly a normal condition as may be possible. In young people, or in older people in whom the arteriosclerotic factor is subordinate to the diabetic factor, an attempt at complete rehabilitation is obligatory. In these two groups every inch of tissue should be spared that can safely be spared with due regard to the demands of good prosthetics. The question to be raised is the desirability of an attempt at complete rehabilitation in older individuals with extensive arteriosclerosis. By complete rehabilitation is meant, of course, the ultimate application of a prosthesis so that the patient can go about his daily affairs with relative ease.

Arteriosclerosis is a progressive disease usually without remissions, presenting a constant threat of spreading thrombosis. We have all had the experience, after the amputation of one extremity, of being forced to amputate the opposite leg by advance of the disease there. As noted earlier, one of the precipitants of gangrene is functional activity.

The question to be raised therefore is whether one is justified in encouraging the activity of an extremity which has not yet come to gangrene by planning and fitting an artificial limb to the opposite stump of amputation. A prosthesis does not restore the patient to normal. The activity of the spared extremity is not comparable to the ordinary amount of work that we commonly think of as being demanded by routine daily activity of the normal individual. A point that has not received wide attention is the fact that the intact extremity of a patient with a leg amputation at any level is subjected to more work than the amount of effort that goes with ordinary activity. If any of you have been on crutches for a time you know how great may be the fatigue of the single available leg. A medical student, young and vigorous, who has had an amputation through the mid lower leg as a result of a war wound and who now has an efficient and comfortable prosthesis, states that the fatigue in his remaining leg with ordinary activity is much greater than in either leg when he had two. The fatigue is greatest when he is on crutches, as he was recently for a few weeks when a furuncle developed on the stump; but it is still present when he is wearing the prosthesis, in spite of the fact that one cannot suspect from gait or stance that he has not two sound legs. The reason for this fatigue is that he has learned certain protective details of locomotion which have become reflex. Any turning motion must be made with the weight on the sound side. The act of going up or down one step, such as a curb, demands for safety that the change be made with the good foot forward. The overwork of the sound leg is painfully evident to him when he finds that the shoe on the normal foot, although covering an elastic and resil-

ient organ, needs half-soling much sooner than the shoe worn on the less pliable prosthesis (Fig. 3). This instance is presented only to support the concept that ordinary locomotion increases the work of the sound leg when one extremity is out of normal commission.

A.



B.

Fig. 3.—Comparison of the wear of shoes worn by an amputee with a mid-tibial stump and a well-fitting prosthesis, demonstrating the greater amount of work performed by the sound foot. Note the thinner sole as shown by the exposed stitches and the crumpling of the vamp as well as its breaking away from the sole.

The problem specifically posed then is whether or not one is hastening the onset of gangrene in the previously unaffected leg by encouraging activity. The problem is not an easy one to consider in the individual case. Of course one must seek partial rehabilitation, to the limit, at least, of the minimal essential demands of independent life such as progress to and from the bed,

the dining-room table, and the toilet. This degree of self-sufficient mobility can be afforded by a crutch life, supplemented by a wheelchair. Should one take the position that an older patient with advanced arteriosclerotic disease is to be relegated to this kind of invalidism in the hope that he will for a longer period of time be able to take care of himself?

Consideration of this question entails discussing the state of the older individual who has lost both legs. The aged can be taught the limited use of crutches fairly safely when one foot is available. In these days of improved prosthetic appliances it is quite possible to fit a young person with bilateral prostheses and to have him use them for a considerable range of activity. I have never personally tried it but I doubt very much that the average arteriosclerotic patient can safely be activated in any manner after bilateral amputation. The fear of falling that comes with the decreasing effectiveness of neuromuscular coordination as age advances is a common clinical observation. We note daily the slowing of pace, the avoidance of rapid turns, and the exaggerated care in negotiating stairs. This fear of falling is not unjustified, as evidenced by the fracture record in the old. It seems to me that it might by itself be a deterrent to the successful use of bilateral prostheses.

Much of this argument involves a priori reasoning but there are enough common observations to indicate that it may be correct. It would require a large series of arteriosclerotic patients over sixty years of age who had been treated with and without a prosthesis with comparison of the interval between amputation of one leg and the onset of gangrene in the other to prove the point. No such study is available, although most authors note the frequency of the sequence.

Of course when any choice of the level of amputation seems to be justified, the whole patient must be considered and not only his extremities. The qualities of courage, serenity, self-control and patience might justify in individual instances an attempt at complete rehabilitation. Certain occupations such as those of a mental worker whose day is spent largely at his desk will influence the decision. Financial and family resources governing the amount of aid that the patient can command at home must also have weight. Other diseases such as a crippled myocardium are a part of the equation. And, finally, both the actual and the apparent physiological age, particularly the quality of neuromuscular coordination, are of importance.

On the whole, in spite of the demonstration that conservation of tissue has become increasingly safe and in spite of the inescapable fact that in younger individuals complete rehabilitation is the ideal goal, I personally am not inclined to adopt attempts to save tissue in the aged arteriosclerotic with or without diabetes. I still cling to the principle that spontaneous sloughing for minor gangrene, with a level at or above the knee for major amputation, is the method of choice in this group of patients. If one believes that the application of a prosthesis to an aged individual is undesirable on the basis of the considerations herein presented, then the need no longer exists for assuming the risk of a second amputation by a first attempt to save the ankle joint or the knee joint.

REFERENCES

1. Mumford, J. G.: The Practice of Surgery, W. B. Saunders Company, Philadelphia, 1910.
2. Buerger, L.: The Circulatory Diseases of the Extremities, W. B. Saunders Company, Philadelphia, 1924.
3. Elkin, D. C., Cooper, F. W., Jr., Rohrer, R. H., Miller, W. B., Jr., Shea, P. C., Jr., and Dennis, E. W.: The Study of Peripheral Vascular Disease With Radioactive Isotopes. I., Surg., Gynec. & Obst. 87: 1-8, 1948.
4. Cooper, F. W., Jr., Elkin, D. C., Shea, P. C., Jr., and Dennis, E. W.: The Study of Peripheral Vascular Disease With Radioactive Isotopes. II., Surg., Gynec. & Obst. 88: 711-718, 1949.
5. Cooper, F. W., Jr.: The Use of Radioactive Isotopes in the Study of Peripheral Vascular Disease, South. M. J. 47: 870-873, 1949.
6. Cooper, F. W., Jr.: Personal communication.
7. Lehman, E. P.: Unpublished data.
8. Shumacker, H. B., Jr., and Moore, T. C.: Leg and Thigh Amputations in Obliterative Arterial Disease, Arch. Surg. 63: 458-465, 1951.

REDUCTION OF THE PERIPHERAL ARTERIAL PULSE BY SPASM OF LARGE ARTERIES

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NEUROGENIC vasospasm is frequently postulated to explain clinical manifestations of reduced blood flow to an extremity or other parts of the body. The typical physiologic mechanism by which such a throttling of blood flow might be produced would involve spasm of the small arterioles. In some instances, however, the spasm is conceived to involve more dominantly the larger muscular arteries. The chief distinguishing characteristic between these two conditions should be manifest in the peripheral pulses. In the absence of any anatomic abnormality in the large vessels, arteriolar spasm of the type observed in Raynaud's phenomenon is accompanied by tissue ischemia without any marked changes in the peripheral pulses. In contrast, large artery spasm should be accompanied by marked reduction or abolition of the peripheral pulses with less evidence of ischemia of the tissues.

There is no doubt that spasm of the larger muscular arteries can occur both clinically[7] and in the experimental animal.[5, 9] The assumption that this can be produced neurogenically by reflex action, however, awaits demonstration. As summarized by Sir Thomas Lewis[6]: "This hypothesis is without anatomical or physiological sanction, and difficult to accept in that large arteries cannot be brought to occlusion and maintained there by sympathetic stimulation." Although Lewis was specifically referring to the production of ischemia, much the same argument can be raised in reference to pulse changes. It takes a great reduction in the lumen of the larger vessels to alter the peripheral pulses significantly[3] and, in general, vasoconstriction has been claimed to augment peripheral pulses.[2, 4] The present study was therefore undertaken in an attempt to demonstrate whether nerve stimulation could evoke sufficient contraction in the muscular arteries of the leg to diminish the dorsalis pedis pulses in anesthetized dogs.

METHODS

To avoid the difficulties in recording and interpreting volume pulses, pressure pulses were recorded directly by introducing short 15 gauge needles into the exposed dorsalis pedis arteries bilaterally and recording the pulses with a Hathaway blood pressure recording system.[8] The pressure pulses in the left leg were used as controls, while attempts to alter the pulse were restricted to the right leg.

Dogs were anesthetized intravenously with α-choralose, using an initial dose of 75 mg. per kilogram followed by supplementary doses of 15 mg. per

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kilogram at thirty-minute intervals. This anesthesia was selected for its lack of depression of vasomotor reflexes. Since blood flow studies were also made in most experiments, the dogs were routinely heparinized with Paritol A.* In order to eliminate mechanical artifacts associated with motor nerve stimulation the animals were curarized (d-tubocurarine chloride) when necessary. Initial surgery was restricted to exposing the dorsalis pedis arteries at the ankles, cannulating a jugular vein for injections, and performing a tracheotomy in order to be prepared to institute artificial respiration after curarization. Pulse recordings were then made which were used as controls to evaluate any pulse changes that might have been associated with the additional surgical procedures.

In order to assess the nature of the general vasomotor response induced by the experimental procedures employed, blood flows were recorded in many experiments by determining the outflow from the femoral vein. This flow was metered by means of the strain gauge flowmeter,[1] and returned to the circulation via the jugular vein. No attempts were made to restrict collateral venous drainage, but the femoral venous outflow was kept at a fixed hydrostatic level of the vena cava so that directional changes in blood flow through the leg should be accurately recorded.

RESULTS

Since clinical evidence would suggest that trauma in the vicinity of a large artery is the most common cause of vasospasm,[7] attempts were made to reproduce this situation experimentally. Exposing the femoral artery in the thigh, pinching it, stripping it, and crushing it were all found to be ineffective in producing any detectable alteration in the dorsalis pedis pulses. Application of intense electrical stimuli of high and low frequencies to the femoral arteries or the surrounding fascia were equally ineffective. Trauma, occlusion, or electrical stimulation of the femoral vein also failed to reveal any evidence of pulse changes. Intra-arterial injections of epinephrine through a small side-branch of the femoral artery did not produce significant changes on the injected side as compared with the opposite side.

In contrast to these negative results, striking changes in the dorsalis pedis pulses could be evoked by direct motor nerve stimulation. The effect was best demonstrated by stimulation of the peripheral end of the cut sciatic nerve on the same side. Typical results, as illustrated in Figs. 1 and 2, could be reproduced in the six dogs studied with the regularity that one anticipates for any nerve-muscle preparation. The nature of the stimuli did not appear critical, since the response could be produced with tetanic shocks from an induction coil or repetitive condenser discharges at frequencies of from ten to one hundred per second. Maximal responses were obtained at the higher frequencies and at peak intensities, measured in situ, of approximately twenty volts.

Fig. 1 illustrates the response to sciatic stimulation with a slow recording speed to demonstrate the over-all nature of the reaction. The upper pulse was obtained from the left dorsalis pedis. The pressures averaged 186/106 and,

*Kindly supplied by Dr. Joseph Seifter of the Wyeth Institute of Applied Biochemistry, Philadelphia, Pa.

except for respiratory variations, remained uniform throughout the recording period. The lower record was obtained from the dorsalis pedis artery of the right leg. Measurement of the control pressures prior to stimulation yielded average values of 184/107. It should be noted that control pressure tended to be somewhat hypertensive, as is typical with chloralose anesthesia. Stimulation of the right sciatic nerve, indicated by the bar over the base line, resulted in a marked lowering of the pulse pressure in the right leg. The maximal fall on this record, averaged for respiratory variations, was a reduction in systolic

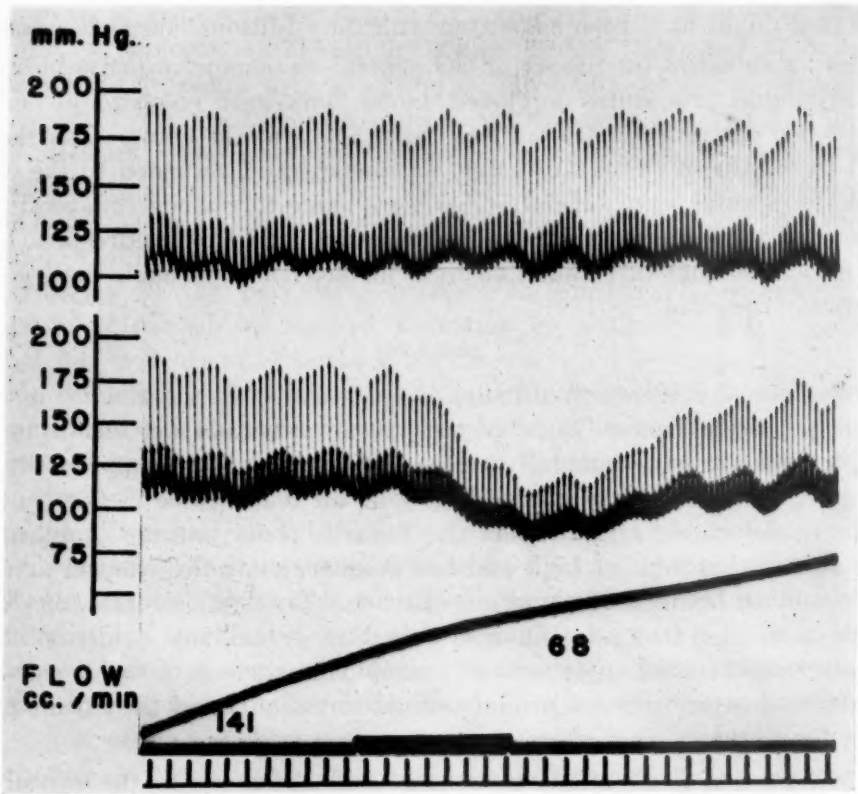

Fig. 1.—Pressure pulses recorded from the dorsalis pedis arteries of an anesthetized dog: Upper tracing is from the left (control) leg; lower tracing is from the right leg. During the interval indicated by the black bar above the base line, the peripheral end of the cut right sciatic nerve was stimulated tetanically. The animal was curarized to prevent skeletal muscle contraction except for a momentary twitch at the onset of stimulation, as may be detected by a jog in the lower pulse tracing.

pressure of 74 mm. Hg and a drop in diastolic pressure of 26 mm. Hg, yielding a blood pressure of 110/81. This represents a change from the original pulse pressure of 77 mm. to a pulse pressure of only 29 mm. Estimates of the mean blood pressure in the right dorsalis pedis indicated a control value of 127 mm. which on stimulation fell to a level of 88 mm. Fig. 2 illustrates pulses from another experiment in which the recording speed was so increased as to demonstrate the changes in pulse contour. Comparison of the control pulse with the pulse recorded during stimulation indicates pressure changes of a similar

nature to those previously described and alterations in pulse contour which appear to be dominantly that of damping, with a marked lowering of the primary peak and a significant reduction in the dicrotic oscillations. In recordings of this type it was possible to measure mean blood pressure accurately by the planimetry method; in this case the control value was found to be 132 mm. Hg which fell on stimulation to a level of 103 mm.

To clarify the nature of the vasomotor response which was occurring in the leg, it appeared of value to obtain blood flow measurements during such experiments. These are included in Fig. 1 where the flowmeter tracing is indicated by the slowly ascending line beneath the pulse tracings; the rate of outflow is indicated by the rate of rise of this line. Actual measurement revealed an initial flow of 141 c.c. per minute which on stimulation was reduced to 68 c.c. per minute. These results make it clear that a dominantly vasoconstrictor response of the arterioles accompanies the observed dampening of the dorsalis pedis pressure pulses.

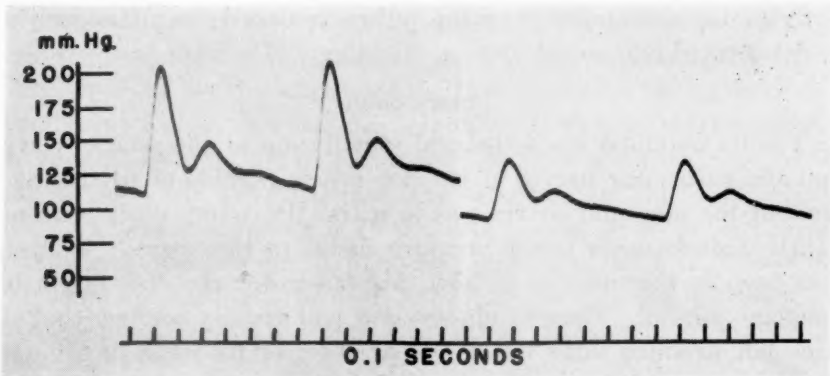

Fig. 2.—High speed recording of pulses to demonstrate change in contour from control pulse (left) to that obtained during sciatic nerve stimulation (right).

An analysis of recordings obtained in other experiments with sciatic stimulation yielded results that were quite similar. The maximal responses obtainable were a reduction in dorsalis pedis pulse pressure to about 25 per cent of the control value and a drop in mean pressure of from 20 to 30 mm. Hg. The blood flow during these maximal responses fell to slightly less than one-half of the control value.

The responses fit the criteria that would be expected of true vasomotor responses. They appeared after a latency of about five seconds and reached their maximum about fifteen seconds after the start of stimulation. The pulses did not return to normal until at least thirty seconds after the stimulus was removed. Proof that they were not caused by mechanical occlusion of the system due to skeletal muscular contraction was obtained by finding that the pulse change persisted after adequate curarization to abolish all skeletal muscular response except for a slight twitch at the moment of initiating the stimulation. Evidence that the end-organ mechanism was the usual vasomotor system was obtained by excessive curarization. With massive doses of curare

the pulse reduction with sciatic stimulation was obtainable only as long as the arterial pressure was reasonably well maintained. When sufficient curare was given to induce vasomotor paralysis, as evidenced by a significant fall in blood pressure, the response to stimulation progressively diminished until, at markedly hypotensive levels, the response completely disappeared. This disappearance of the response with curare poisoning appeared to be due to vasomotor paralysis rather than to any action of the hypotension itself, since inducing comparable levels of hypotension by bleeding the animals revealed no such obliteration of the response to sciatic stimulation.

Stimulation of the femoral nerve gave a response which produced a slight reduction in dorsalis pedis pulses, but at no time approached the magnitude of the changes observed with sciatic nerve stimulation. Repeated attempts to elicit a reduction in peripheral pulses reflexly have so far been unsuccessful. Afferent stimulation did have marked effects, of course, in altering general blood pressure, heart rate, and blood flow, but no evidence was obtained of significant differences between the pulses observed during such stimulation from an innervated leg as compared to the pulses recorded simultaneously from the opposite denervated leg.

DISCUSSION

The results obtained by peripheral stimulation of the sciatic nerve make it clear that the vasomotor nerves of the dog are so capable of producing an effective spasm of the muscular arteries as to markedly reduce peripheral pulses and significantly reduce mean blood pressure distal to the spasm. As yet, no evidence has been forthcoming as to how this vasomotor response might be elicited by physiologic stimuli. Careful observation will readily confirm that trauma of the vessel can produce some visible constriction of its walls in the area stimulated,[5] but in the present experiments such local constrictions were not sufficient to alter the transmitted pulse pressures. This would indicate that any reflexes associated with this local trauma were not able to elicit the acute generalized spasm of the femoral system as was obtained by motor nerve stimulation.

Since the flow of blood through the hind leg was observed to decrease by 50 per cent while the mean arterial pressure in the dorsalis pedis artery was reduced only 20 per cent, it seems probable that the change in blood flow was due largely to coincidental arteriolar constriction rather than to the large artery spasm itself. The present findings, therefore, have not demonstrated a spasm of muscular arteries of sufficient intensity to account for the peripheral ischemia which is often attributed to large artery spasm observed clinically. It must be recognized, however, that the clinical cases in which large artery spasm is assumed to occur are often complicated by diseased vessels, edema of the tissues, or other factors which would all tend to exaggerate the degree of ischemia produced by a moderate drop in perfusion pressure.

These results obtained with sciatic stimulation upon the peripheral pulses are in interesting contrast to the observations reported by Kinmouth and associates[5] on changes in the diameter of the femoral artery. They were unable to produce a measurable change in the diameter of the femoral artery by nerve

stimulation, but were able to elicit a constriction of the artery by direct trauma. The latter effect persisted after denervation of the sympathetic outflow to the limb, suggesting that there may be a local mechanism acting on the blood vessels in addition to the effects observed here with sciatic stimulation. Such a mechanism might explain observations which we have made on some thirty dogs in which dorsalis pedis pulses have been recorded. After three to four hours of various experimental procedures, difficulty has often been encountered in obtaining dorsalis pedis pulses free from evidence of damping. This has not appeared to be associated with any technical defect in the recording system and persists after denervation of the limb. This suggests that there might be some mechanism for inducing spasm of the muscular arteries which cannot be readily demonstrated in acute experiments. Studies of this mechanism in chronic experiments might prove to be of value.

SUMMARY

Possible factors capable of inducing spasm of the larger muscular arteries have been searched for by recording the dorsalis pedis pulses bilaterally in the anesthetized dog, employing the pulse in the left leg as a control while various stimuli were applied to the right leg. Direct trauma or various forms of reflex stimulation failed to elicit any significant change in the pulse. Definite pulse changes were observed, however, with direct motor nerve stimulation. Maximal responses recorded from the experimental side with sciatic nerve stimulation were accompanied by a 75 per cent reduction in pulse pressure and a 20 per cent reduction in mean pressure, associated with a 50 per cent decrease in blood flow through the leg. The possible bearing of these observations upon large artery spasm observed clinically is discussed.

REFERENCES

1. Alexander, R. S.: *In Vivo* Observations on the Distensibility of the Femoral Venous System, Proc. Soc. Exper. Biol. & Med. **67:** 410, 1948.
2. Alexander, R. S., and Webb, E. A.: An Analysis of Changes in the Contour of the Femoral Arterial Pulse During Hemorrhagic Shock, Am. J. Physiol. **150:** 272, 1947.
3. Gupta, T. C., and Wiggers, Carl J.: Basic Hemodynamic Changes Produced by Aortic Coarctation of Different Degrees, Circulation **3:** 17, 1951.
4. Hamilton, W. F.: The Patterns of the Arterial Pressure Pulse, Am. J. Physiol. **141:** 235, 1944.
5. Kinmonth, J. B., Simeone, F. A., and Perlow, V.: Factors Affecting the Diameter of Large Arteries With Particular Reference to Traumatic Spasm, SURGERY **26:** 452, 1949.
6. Lewis, T.: Vascular Disorders of the Limbs, Described for Practitioners and Students, ed. 2, London, 1949, Macmilian & Co.
7. Montgomery, A. H., and Ireland, J.: Traumatic Segmentary Arterial Spasm, J. A. M. A. **105:** 1741, 1935.
8. Schafer, P. W., and Shirer, H. W.: An Impedance Gauging System for Measurement of Biological Pressure Variables, SURGERY **26:** 446, 1949.
9. Solis, J. T., and Essex, H. E.: Action of Protamine Sulfate and Certain Other Drugs on the Vascular System of the Rabbit, Am. J. Physiol. **167:** 1, 1951.

A MODIFIED POTTS BULLDOG CLAMP FOR USE IN PORTACAVAL SHUNTS

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PORTAL hypertension with its associated esophageal varices still presents a therapeutic challenge. Within the last ten years many technical advances have been made in the experimental laboratory, some of which have stood the test of clinical application. Foremost among these are the shunt operations of Blakemore, Linton, and others. These are either the direct portacaval or the lienorenal type. Along with development of these operative techniques, numerous vascular clamps have been employed for the control of blood flow during the suture anastomosis. Among these are the Potts-Smith, Blalock, Satinsky, Freeman, and Southwick clamps. In this communication we are reporting our modification of the Potts bulldog clamp.† We feel that this clamp has several advantages over those commonly in use.

The type of clamp in which a flat surface is placed in contact with the vein wall in order to hold the vessel without leakage or slipping, is likely to result in a certain amount of crushing. This was recognized as early as 1903 by Carrell. Damage to the vein wall, and especially the intima, may be sufficient to serve as a nidus for thrombus formation, or may even cause necrosis. We have observed this in experimental animals. An interdigitating toothed clamp (Potts principle) of the Freeman or Southwick type requires a minimum of pressure to control bleeding and prevent slipping. It causes no damage to the vein since no two pressure points are directly opposed. However, both clamps have long handles which may, under certain conditions, obscure the operative field and may also limit the space necessary to perform a good anastomosis. It may be difficult, because of the long handles, to apply them adequately to vessels in the depths of a small operative field. In addition, they may be accidentally dislodged.

To circumvent these objectionable features, we have modified the standard Potts bulldog clamp. The standard clamp occludes only a portion of the vein wall, thus permitting adequate blood flow around the clamp and requiring minimal dissection of the vessel. However, the length of segment of vein wall grasped is not sufficient to allow an anastomosis of the size necessary to reduce portal pressure adequately. For this reason, the modified clamp is made twice

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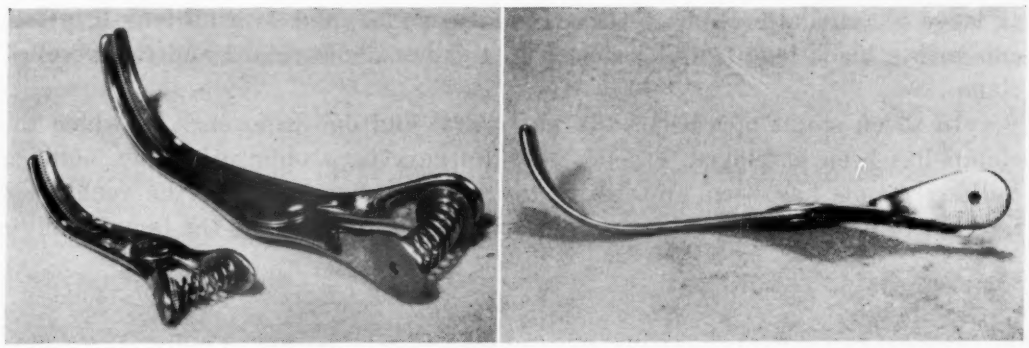
†Made to our specifications by B. Richter, Glen Ellyn, Ill.



A. *B.*

Fig. 1.—*A*, Comparison of the standard Potts bulldog clamp with the enlarged modification. Note the fine interdigitating teeth and the thumb screw which permits minute variations in the pressure of application.

B, Demonstration of the arc of the blade which allows anastomoses from 1 to 2 cm. in diameter to be established.

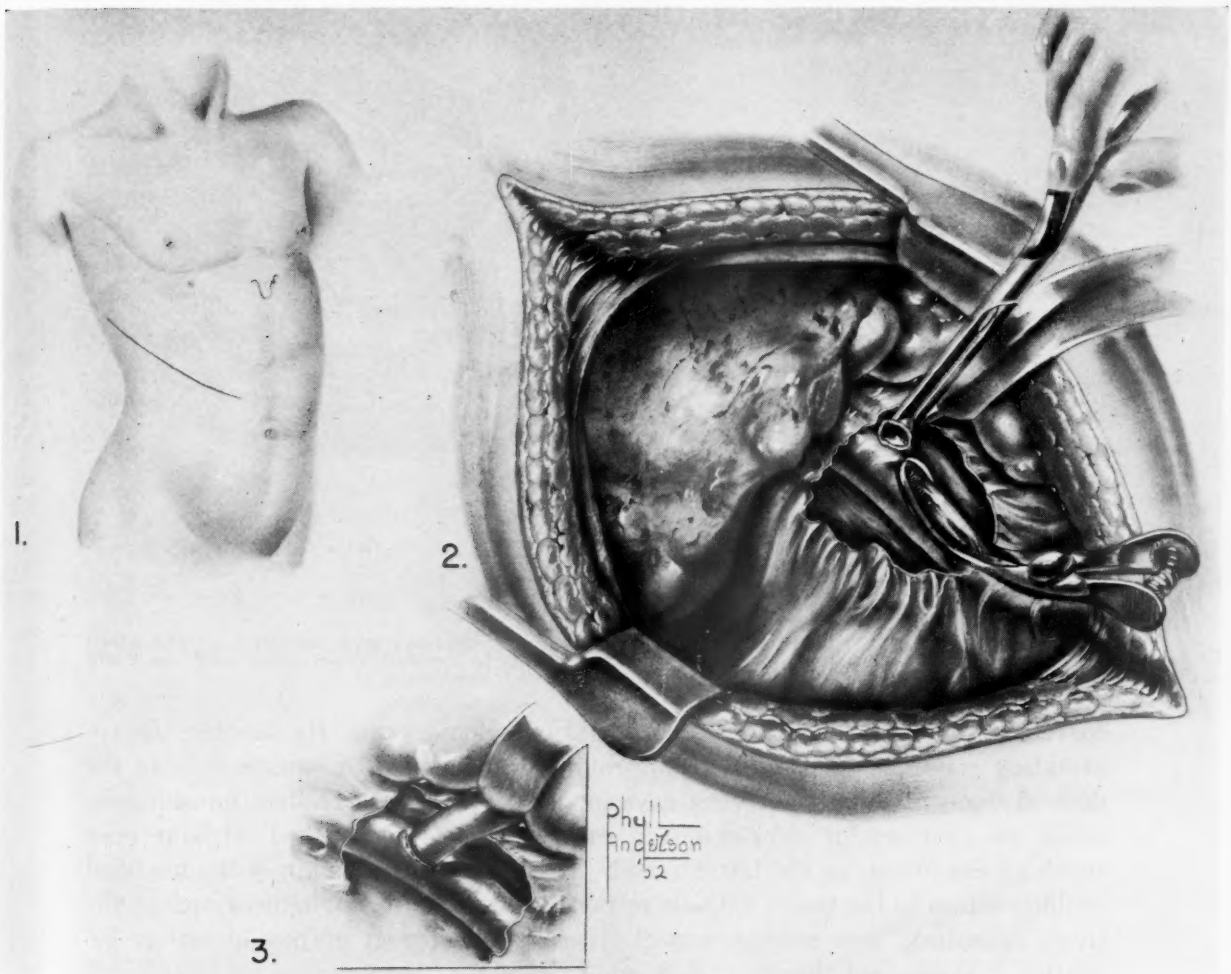


Fig. 2.—Use of the clamp in a direct portacaval shunt. *1*, Incision with resection of the eighth rib, *2*, application of the modified Potts bulldog clamp to the inferior vena cava and the Potts coarctation clamp to the portal vein, *3*, the completed anastomosis.

as large without alteration of the arc of the blade. The over-all length is 11.4 cm. with a blade length of 4.4 cm. Fig. 1 shows the standard and the modified clamp.

In seven shunt operations, six portacaval and one lienorenal, in which the clamp has been employed, excellent results have been obtained. The modified bulldog clamp has been applied to the inferior vena cava or the renal vein parallel to its axis without obstructing more than one-third of the lumen. Potts

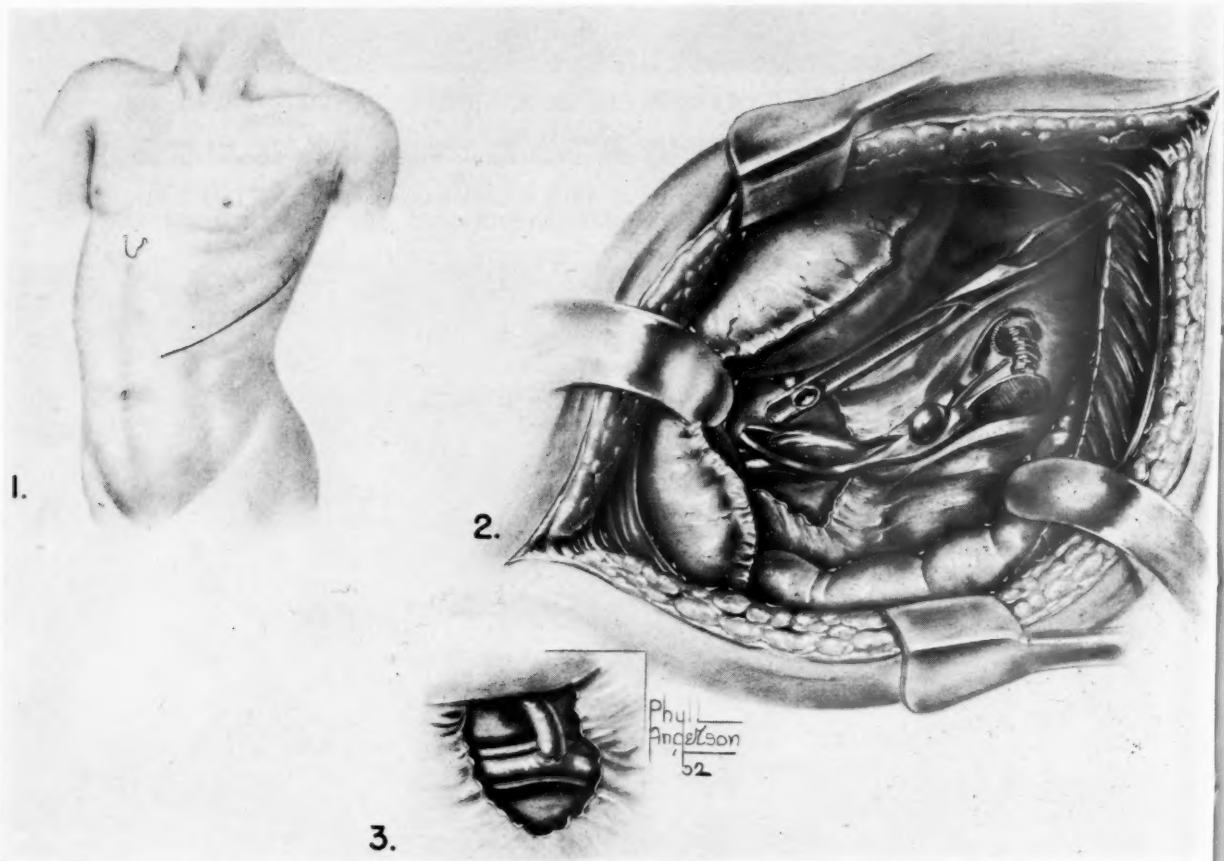


Fig. 3.—Use of the clamp in a lienorenal shunt. *1*, Incision with resection of the ninth rib, *2*, application of the modified Potts bulldog clamp to the left renal vein, and the Potts coarctation clamp to the splenic vein, *3*, the completed anastomosis.

coarctation clamps are used on the portal or splenic vein. By holding the coarctation clamp, it is possible to approximate the portal or splenic vein to the desired segment of inferior vena cava or renal vein. An excellent anastomosis, using an everting or over-and-over suture, can be established without once touching the clamp on the latter vessel. It is also possible to apply the modified bulldog clamp to the vessel without retracting surrounding structures such as the liver, intestines, and retroperitoneal tissues. The threat of postoperative distention is minimized thereby. Following removal of both clamps we have never observed indentation or other evidence of damage to the vessel at the site of application. Figs. 2 and 3 demonstrate the use of the clamp in both the direct

portacaval and the lienorenal type of anastomosis. It will be noted that the curve of the clamp permits formation of shunts ranging from 1 cm. to 2 cm. in diameter.

SUMMARY

A modification of the Potts bulldog clamp for adaptation to portacaval shunt procedures and the technique of its application have been described. The advantages over the commonly used clamps for this operative procedure are listed.

ADDENDUM

Since this article was submitted for publication, the clamp has been successfully used in fourteen additional porta caval shunt operations.

CLOSURE OF ATRIAL SEPTAL DEFECTS WITH THE AID OF HYPOTHERMIA; EXPERIMENTAL ACCOMPLISHMENTS AND THE REPORT OF ONE SUCCESSFUL CASE

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IN THE past the use of general or regional refrigeration in clinical medicine has been disappointing. Despite the fact that Fay,[13] a number of years ago, stimulated interest in the therapeutic potentialities of hypothermia when he reported on its use as a palliative method for treating patients with advanced cancer, little evidence developed to show that his method was better than the more simple treatments for incurable cancer, and it was never widely used. A little later, regional refrigeration, used as a preservative and anesthetic agent in treating gangrenous or severely wounded extremities, received consideration[9, 10] and many articles were published concerning the technique, but this method seems no longer to be of interest. Other anesthetic agents are better.

Despite these failures, it might still be expected that the production of greatly lowered body temperature would find use in medicine. The strikingly reduced metabolic rates associated with states of hibernation or artificially induced hypothermia[1, 3, 4] offer intriguing possibilities for the performance of operations requiring relatively prolonged vascular occlusion. A rewarding exploration of some of these possibilities has been undertaken by Bigelow,[2, 4] who has experimentally demonstrated the potentialities of hypothermia as an aid in cardiac surgery. He showed that during profound hypothermia in the dog, a longer cardiac inflow occlusion was possible than was tolerated without danger at normal body temperature. This maneuver made possible a cardiotomy in a dry field allowing examination of the interior of the heart for a number of minutes without the aid of complicated pumps or shunting procedures. With the body temperature reduced to 20° C., 51 per cent of his dogs, including 11 which had a cardiotomy during the operation, survived a fifteen-minute period of total cardiac inflow occlusion.

Boerema[6] also has used body cooling in dogs for the performance of intracardiac operations. In a number of animals the circulation was interrupted for ten to twenty minutes and in four dogs portions of the atrial septum were removed.

It has been our purpose to continue in this direction, using hypothermia experimentally as an aid for the production and correction of intracardiac defects under direct vision. We have tried to make the technique simple and safe enough so that its use for the closure of similar defects in human beings

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would be possible. Our experimental efforts to date have been concerned with the production and closure of atrial septal defects. It is sensible to work with this lesion first, for of the various intracardiac lesions which demand some kind of plastic repair for their correction it is probably the simplest to deal with. Experience gained in treating this lesion might later be directed toward the more difficult ventricular septal and aortic valve defects. Furthermore, ability to correct atrial septal defects in human beings would have great practical value, for this is a frequent and disabling congenital cardiac defect.[12, 18]

Atrial septal defects have been closed experimentally by a number of blind techniques[8, 14, 16-18, 20] and some of these methods have been used in clinical cases. Closure of the defect under direct vision, a more deliberate approach, has been attempted clinically at this hospital with a heart lung apparatus, but the patient did not survive.[11]

EXPERIMENTAL METHODS

It was planned to submit each of the adult mongrel dogs used in these experiments to two operations. At the first operation a large atrial septal defect was made under direct vision, then after a recovery period of a week or longer, the heart was re-entered and the defect was closed.

Production of Defects.—For each operation, either to make or to close the defects, the same cooling technique was used. The dog was first anesthetized with Pentothal Sodium and then cooled by wrapping the entire animal in rubberized blankets through which flowed a cold alcohol solution.* The trachea was intubated and, when respiration became shallow, artificial respiration was started, utilizing an automatic respirator. The rectal temperature and the pulse rate fell gradually over a period of one to two hours from a normal temperature of 38° C. and a pulse rate of 160 to 180 down to a temperature of 26 to 28° C. and a pulse rate of 50 to 70.

At that point the blankets were partially removed and the chest was entered through the right fourth interspace. The azygos vein was ligated and the inferior and superior venae cavae were isolated and each was encircled with a double loop of heavy silk. Though Procaine or no local anesthetic had been used earlier, later in the series, 3 to 4 c.c. of 1 per cent butacaine sulfate (Butyn Sulfate) was injected into the pericardial sac and allowed to remain there for five minutes before direct manipulation of the heart was begun, as has been recommended by Bill and Wagner.[5] After this the pericardium was opened. When we were ready to open the right atrium, the loops of silk were tightened occluding both cavae and, during more recent operations, a Satinsky vena cava clamp was applied to the base of the heart occluding the pulmonary artery, the aorta, and the origins of both coronary arteries. This was accomplished by inserting one blade of the clamp through the transverse sinus of the heart.

The right atrium was opened through a longitudinal incision, any remaining blood was evacuated, and the interior was explored. Then the greater part of the membranous septum was removed, creating a large defect through which

*The cooling apparatus, similar to the one used by Bigelow,[2] was made by the Therm-O-Rite Products Corporation, Buffalo, N. Y.

the index finger could be introduced with ease. Following this, the heart was closed with a running stitch of 000 silk and as this stitch was being placed, at least in all but the earlier operations, the heart was filled rapidly with saline through a polythene catheter which was left in the atrium as the stitches were drawn up. Filling of the heart in this manner allowed evacuation of all the air remaining within the chambers. Essential to this method of removing the air during closure was the occlusion of all cardiac outflow with the Satinsky clamp. Without occlusion of the outflow channels, a foam of air and liquid would be ejected into the great vessels during closure of the atrium even though a rapid filling of the heart with blood or saline was attempted just before the atrial wall was approximated.

Closure of Septal Defects.—Actually these precautions against air embolism seemed to be more essential during closure of atrial septal defects than they were during production of the defects. When the defects were closed, the right atrium was opened through the same wound which had been used previously and then the defect was identified and closed with a running stitch of 000 silk. During this closure, the polythene catheter was introduced through the defect into the left atrium for the purpose of injecting saline rapidly into this chamber to wash out any residual air. This was an important step, for even a very small amount of air remaining within the left atrium after its closure seemed to find its way into the coronary arteries when circulation was restarted. The result of that accident was usually fatal.

After completion of the operation either for production or closure of a septal defect, the animal was rewarmed with the same apparatus which had been used to cool him. For rewarming, the alcohol solution was heated before it was pumped through the rubberized blankets. Lately, in other cooling experiments not reported here, we have rewarmed the dogs by immersing them in hot water.

At varying periods following the second operation the animals were sacrificed so that observations on the healing of the septal wounds could be made.

RESULTS

Production of Septal Defects.—Production of atrial septal defects was attempted in thirty-nine animals and of these twenty-seven survived the procedure, an immediate mortality rate of 31 per cent. Of these twenty-seven survivors, one died two days postoperatively with a hemiplegia but the remaining twenty-six lived and were subjected to a second operation for closure of their septal defects. The results are summarized in Table I.

TABLE I. PRODUCTION AND CLOSURE OF ATRIAL SEPTAL DEFECTS

	NUMBER OF DOGS	SURVIVORS	DEATHS	CAUSE OF DEATH		
				VENTRICULAR FIBRILLATION	TECHNICAL ERROR	INDEFINITE
Production	39	27	12	8*	2	2
Closure	26	18†	8	4‡	3	1

*Coronary air embolism occurred in five of these dogs.

†In one of these the defect had closed spontaneously; seven recovered from ventricular fibrillation.

‡Coronary air embolism occurred in two of these dogs.

Ventricular fibrillation occurring during surgery was a prominent cause of death among the twelve animals which failed to survive the operations for the production of atrial septal defects, for eight of the twelve died of this complication. In five animals the ventricular fibrillation was associated with coronary air embolism while in the other three no air was noticed in the coronary arteries. Two animals died because of technical errors and the remaining two deaths occurred during and shortly after surgery, apparently due to cardiac standstill. Among the eight animals which suffered ventricular fibrillation, cardiac massage was effective in restoring a regular beat temporarily in six, but none of them recovered. Electrical defibrillation was not used on these animals.

Closure of Septal Defects.—Twenty-six dogs with atrial septal defects then became candidates for the more difficult operation of closing the defect. Of these, one which had had its septal defect made two and one-half months earlier was found to have a healed defect at the second operation, hence the heart was closed without attempting further surgery. Spontaneous closure of the defect was not noted in the remaining animals, probably because the interval between operations was purposefully kept short. Four dogs died during anesthesia or cooling before the heart was opened, thus leaving twenty-one animals which actually had their septal defects closed. Seventeen of these survived the surgery. Among the eight operative deaths, technical errors were responsible for three, one dog died of indefinite causation, and four died of ventricular fibrillation. In two of the four which succumbed to ventricular fibrillation there was coronary air embolism.

Regarding the problem of ventricular fibrillation, it is of further interest that seven other animals which developed ventricular fibrillation during surgery survived. In two of these the fibrillation was brought on by coronary air embolism while in five no air was present in the coronary arteries. Electrical defibrillation was important in the recovery of two of the dogs, while the other five recovered after periods of massage lasting from five to thirty-five minutes.

Most of the deaths in the series occurred early before the technique now used was evolved. Lately the operations have been quite safe; among the last ten attempts at the production of a septal defect there was only one death and similarly only one death among the last ten operations for closure of the defects.

When the animals were finally sacrificed, the septal defect was found to be soundly healed in every case. In the early postoperative period a small firm thrombus would be found over the wound but later there would be only a smooth endothelial-covered scar. A healed atrial wound is shown in Figs. 1 and 2.

DISCUSSION

The low mortality rate for the operations performed recently is attributable largely to the gradual development of a better technique. The success of the present technique appears to be based primarily on its ability to prevent the accident of coronary air embolism, a frequent cause of ventricular fibrillation early in the series. In developing the operative procedure, we have also been concerned with the occurrence of ventricular fibrillation not related to air

Fig. 1.

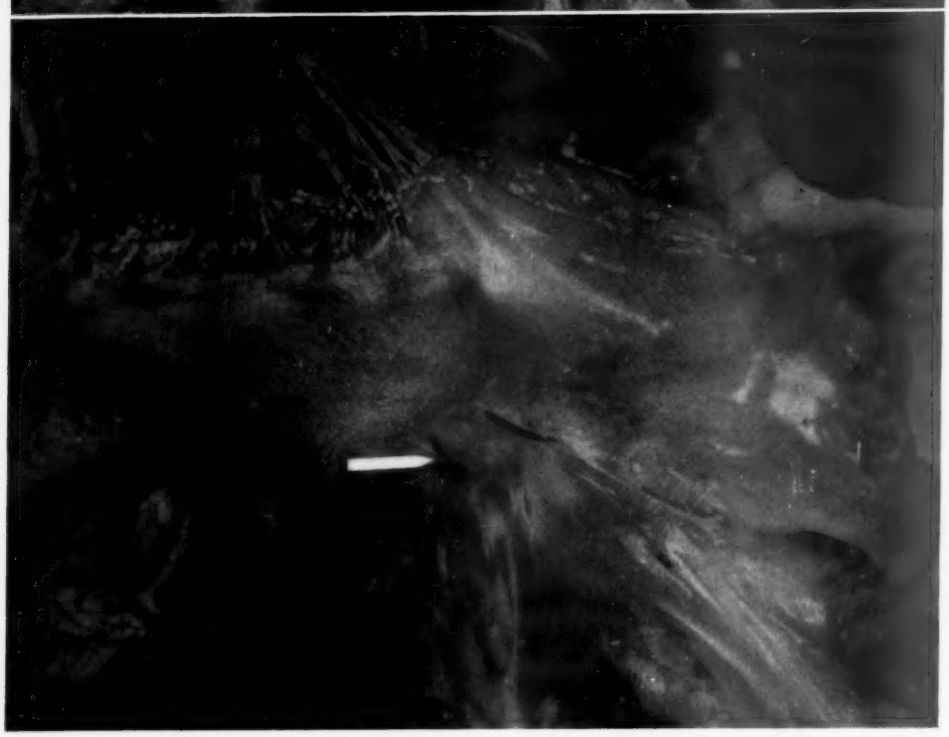

Fig. 2.

Fig. 1.—The atrial wall, viewed from the right atrium, two and one-half months after the defect was closed with a continuous silk stitch. The scar is seen just to the left of the coronary sinus.

Fig. 2.—The same heart shown in Fig. 1 viewed from the left atrium. From this side the endothelial-covered stitches are visible.

embolism. In preventing this type of fibrillation we have not, as yet, been completely successful, but its treatment with electrical defibrillating shocks has often been lifesaving.

Air Embolism.—Air embolism is very likely to occur during or immediately after any operation in which the heart is opened. Though small amounts of air are tolerated by the pulmonary circulation without difficulty, even a minute amount remaining within the left heart may find its way into the coronary arteries with fatal results. The difficulty and importance of avoiding this complication during open intracardiac surgery has been emphasized by other investigators.[7, 17, 19] If success is to be achieved, methods must be developed to avoid coronary air embolism during open intracardiac surgery whether it is performed with refrigeration or by any other technique.

The use of a Satinsky clamp to occlude the outflow of the heart while it is open, as previously described, has been successful in almost completely eliminating air embolism when operating upon the atrial septum. Though it occurred seven times in the first twenty-nine operations, during which the heart was opened either to make or close defects, coronary air embolism happened only twice in the last thirty operations performed with use of the Satinsky clamp. These two failures occurred when the outflow clamping method was first used; later, with better application of the clamps, there has been less danger. In fact, there has been no coronary air embolism during the last twenty-one operations. Proper application of the occluding clamp seems to be important; it should be applied low enough to occlude the coronary arteries if possible. Occlusion of the aorta alone beyond the origin of the coronary arteries was not always adequate to prevent coronary air embolism even though the heart was well filled at the time of closure. In this case air probably escaped beyond the aortic valve while the heart was still open.

Ventricular Fibrillation Not Associated With Air Embolism.—Even when air embolism is eliminated, ventricular fibrillation may still occur. Once started this type is more easily interrupted than that associated with air embolism, but prevention has been difficult. We have tried to reduce its incidence by avoiding the profound reduction in body temperature used by Bigelow[2, 4] and by the use of local anesthetics within the pericardium.

The temporary anoxia which occurs during inflow occlusion supplemented by the cardiac trauma which occurs during manipulation may be sufficient to cause fibrillation in these cases, but there is, in addition, the possibility that cold itself is a further predisposing cause. Bigelow's work suggests that this may be true at least for body temperatures of 20° C. or lower,[2, 4] and another investigator has concluded that cold increases the sensitivity of the ventricles to fibrillation.[15] A study of the effects of various degrees of hypothermia on ventricular irritability has not been done, but, nevertheless, we felt that it would be safer to use somewhat higher body temperatures than Bigelow did. Even at the temperatures we used, a cardiac inflow occlusion is tolerated for a sufficient length of time to allow the performance of intracardiac procedures under direct vision.

Butacaine sulfate applied topically has been advocated as a more effective agent than procaine for reducing the irritability of the heart muscle.[5] Though we have no controlled data concerning butacaine's effectiveness, in our experience fibrillation has occurred only following its use, when topical application has been difficult due to the rent in the pericardium made at previous surgery.

CLOSURE OF AN ATRIAL SEPTAL DEFECT IN A CLINICAL PATIENT

This is a preliminary report on the successful closure of an atrial septal defect in a 5-year-old child using the same technique we have employed in dogs. When we felt that the method had reached the stage where clinical trial was justified, Dr. R. L. Varco kindly sought and found a suitable candidate for the operation.*

The patient (University Hospital No. 843410) was an underdeveloped, sickly, 29½ pound, 5-year-old girl in whom the diagnosis of an atrial septal defect had been established by cardiac catheterization. On Sept. 2, 1952, she was anesthetized with Pentothal Sodium and curare and the trachea was intubated. She was then wrapped in the refrigerated blankets until, after a period of two hours and ten minutes, her rectal temperature had fallen to 28° C. (82° F.). At this point the blankets were removed and the chest was entered through the bed of the right fifth rib. The cardiac inflow was occluded for a total of five and one-half minutes and during this time a septal defect measuring approximately 2 cm. in diameter was closed under direct vision, in the manner described in the section on experimental method. In one respect the procedure was easier than it had been in dogs, for the right atrium was more dilated and hence roomier to work in. When the Satinsky clamp and ligatures had been removed, the pulse promptly regained its strength.

At the conclusion of the operation, which lasted fifty-eight minutes, the patient's rectal temperature was 26° C. (79° F.). To rewarm her she was placed in hot water kept at 45° C. (113° F.), and after thirty-five minutes her rectal temperature had risen to 36° C. (96.8° F.) at which time she was removed from the bath. Recovery from the anesthesia was prompt and her subsequent postoperative convalescence has been uneventful. She left the hospital on the eleventh postoperative day. Her cardiac murmur is gone.

SUMMARY

1. In dogs, atrial septal defects were made and subsequently closed under direct vision with the aid of hypothermia. Body temperature of the animals was reduced to 26 to 28° C. rectally. With the right atrium open, a dry field was obtained by temporarily occluding the superior and inferior venae cavae for periods of time up to eight minutes.

2. Production of atrial septal defects was attempted in thirty-nine animals and there were twenty-seven survivors. Among the last ten attempts there were nine survivors. Twenty-six of the survivors had operations for closure of the defects, and in seventeen the defects were successfully closed and the animals survived. In nine of the last ten attempts at closure the animals lived.

3. The occurrence of ventricular fibrillation was the most harassing complication encountered. Its incidence has been reduced by the adoption of measures designed to prevent the development of coronary air embolism during the surgery.

*The authors wish to acknowledge their appreciation of Dr. R. L. Varco's sympathetic and helpful interest in the project.

4. The successful closure under direct vision of an atrial septal defect in one clinical case is reported. For this case the same technique as that used in the dogs was employed.

REFERENCES

1. Benedict, F. G.: Hibernation and Marmot Physiology, Washington, D. C., 1938, Carnegie Institution, pp. x, 239.
2. Bigelow, W. G., Callaghan, J. C., and Hopps, J. A.: General Hypothermia for Experimental Intracardiac Surgery, Ann. Surg. 132: 531-539, 1950.
3. Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gordon, R. A., and Greenwood, W. F.: Oxygen Transport and Utilization in Dogs at Low Body Temperatures, Am. J. Physiol. 160: 125-137, 1950.
4. Bigelow, W. G., Lindsay, W. K., and Greenwood, W. F.: Hypothermia; Its Possible Role in Cardiac Surgery, Ann. Surg. 132: 849-866, 1950.
5. Bill, A. H., and Wagner, J. C.: A Method for the Prevention of Ventricular Fibrillation During Operation on the Heart, Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, Philadelphia, 1950, W. B. Saunders Company, p. 217.
6. Boerema, I., Wildschut, A., Schmidt, W. J. H., and Broekhuysen, L.: Experimental Researches Into Hypothermia as an Aid in the Surgery of the Heart, Arch. chir. neerl. 3: 25-34, 1951.
7. Clowes, G. H. A.: Experimental Procedures for Entry Into the Left Heart to Expose the Mitral Valve, Ann. Surg. 134: 957-968, 1951.
8. Cohn, R.: An Experimental Method for the Closure of Interauricular Septal Defects in Dogs, Am. Heart J. 33: 453-457, 1947.
9. Crossman, L. W., and Allen, F. M.: Surgical Refrigeration and Preservation of Tissue, J. A. M. A. 133: 377-382, 1947.
10. Crossman, L. W., Ruggiero, W. F., Hurley, V., and Allen, F. M.: Reduced Temperatures in Surgery, Arch. Surg. 44: 139-156, 1942.
11. Dennis, C., Spreng, D. S., Nelson, G. E., Karlson, K. E., Nelson, R. M., Thomas, J. V., Eder, W. P., and Varco, R. L.: Development of a Pumpoxygenator to Replace the Heart and Lungs; an Apparatus Applicable to Human Patients, and Application to One Case, Ann. Surg. 134: 709-721, 1951.
12. Dry, T. J.: Atrial Septal Defects, M. Clin. North America 32: 895, 1948.
13. Fay, T.: Observations on Prolonged Human Refrigeration, New York State J. Med. 40: 1351-1354, 1940.
14. Gross, R. E.: Informal presentation at the University of Minnesota Medical School (April, 1952).
15. Hoff, H. E., and Stansfield, H.: Ventricular Fibrillation Induced by Cold, Am. Heart J. 38: 193-204, 1949.
16. Hufnagel, C. A., and Gillespie, J. F.: Closure of Interauricular Septal Defects, Bull. Georgetown Univ. M. Center 4: 137-139, 1951.
17. Martin, W. B., and Essex, H. E.: Experimental Production and Closure of Atrial Septal Defects, With Observations of Physiologic Effects, SURGERY 30: 283-297, 1951.
18. Murray, G.: Closure of Defects in Cardiac Septa, Ann. Surg. 128: 843-853, 1948.
19. Potts, W. J., Riker, W. L., DeBord, R., and Andrews, C. E.: Maintenance of Life by Homologous Lungs and Mechanical Circulation, SURGERY 31: 161-166, 1952.
20. Swan, H., Maresh, G., Johnson, M. E., and Warner, G.: The Experimental Creation and Closure of Auricular Septal Defects, J. Thoracic Surg. 20: 542-551, 1950.

OBTURATION OF THE DUODENUM AS AN AID IN CHOLANGIOGRAPHY

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THE purpose of this communication is to describe a method which increases the information obtainable from cholangiography. The procedure involves occlusion of the outlet of the common bile duct into the duodenum by means of an air-inflated balloon at the time of the injection of the radiopaque dye through the tube previously inserted into the common duct at operation.

PROCEDURE

A 3½ inch long thin rubber balloon, fitted over the distal end of an Abbott-Rawson[1] tube (Fig. 1), is introduced into the second portion of the duodenum under fluoroscopic guidance. The tube at its emergence from the mouth is anchored to the cheek by adhesive tape. The balloon is inflated with sufficient air (about 75 ml.) to obturate the lumen of the duodenum but not enough to give rise to the pain of excessive distention. The radiopaque material is then injected into the ductal system through the common duct tube and roentgenograms are made in the usual manner.

The Abbott-Rawson type of tube was used for the intubation procedure, but any other type of tube would accomplish the objective provided its lumen had free communication with the balloon for the introduction or withdrawal of air. The Abbott-Rawson tube arrangement is convenient because its gastric lumen permits the introduction of procaine or other solutions sometimes used to facilitate passage of the tube through the pylorus.

RESULTS

CASE 1.—R. M., a 51-year-old white housewife, developed an "obstructive" type of jaundice four months following cholecystectomy at another hospital. Three months later she experienced bouts of fever and chills and complained of generalized pruritus. She was subjected to laparotomy but her symptoms were not relieved. She was admitted to the General Surgical Service of the Hospital of the University of Pennsylvania a year later and was explored. A choledochoduodenostomy was taken down and an obstructing stricture of the common bile duct repaired over a T tube. The distal limb of the T tube extended from the common duct through the sphincter of Oddi into the duodenum. Despite an uneventful postoperative course and the drainage of clear bile out of the T tube, the intensity of the icterus did not lessen. During the next nine months cholangiography[2, 3] was performed six times. On each occasion the dye promptly entered the duodenum and the biliary radicles above the common duct failed to be visualized (Fig. 2*A*).

The patient was subsequently intubated and a balloon inflated in the duodenum in order to prevent the radiopaque dye, introduced through the common duct tube, from enter-

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ing the duodenum. This time the entire biliary tract as well as the main pancreatic duct was visualized (Fig. 2*B*). A filling defect was noted in the left hepatic duct. The patient was re-explored and three stones and sediment were removed from the left hepatic duct. The icterus lessened promptly following operation but did not disappear entirely.

CASE 2.—J. K., a 65-year-old white man, was found to have an enormous hydrops of the gall bladder and marked dilatation of the common bile duct at laparotomy. The gall bladder and its contained stones were removed. The common bile duct was opened, explored, and stones were extracted. An attempt to pass a probe through the common duct into the duodenum was unsuccessful because of fibrosis and constriction of the sphincter of Oddi. The sphincter was incised and a T tube inserted into the common bile duct with its distal arm passing through the sphincter into the duodenum. The common bile duct was then closed.

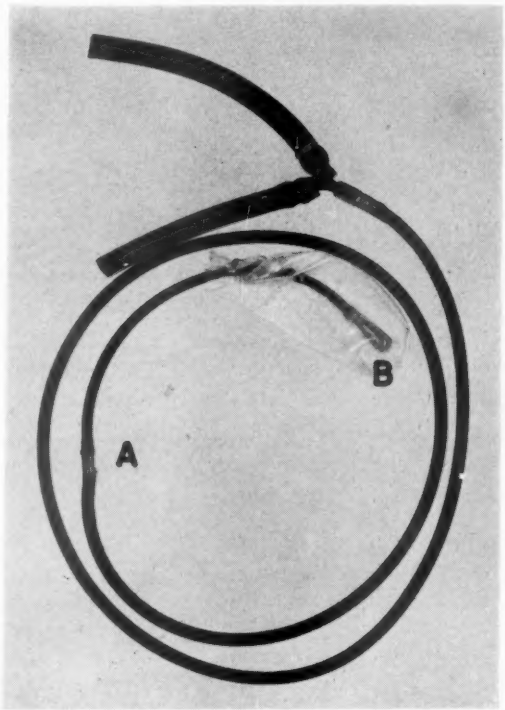
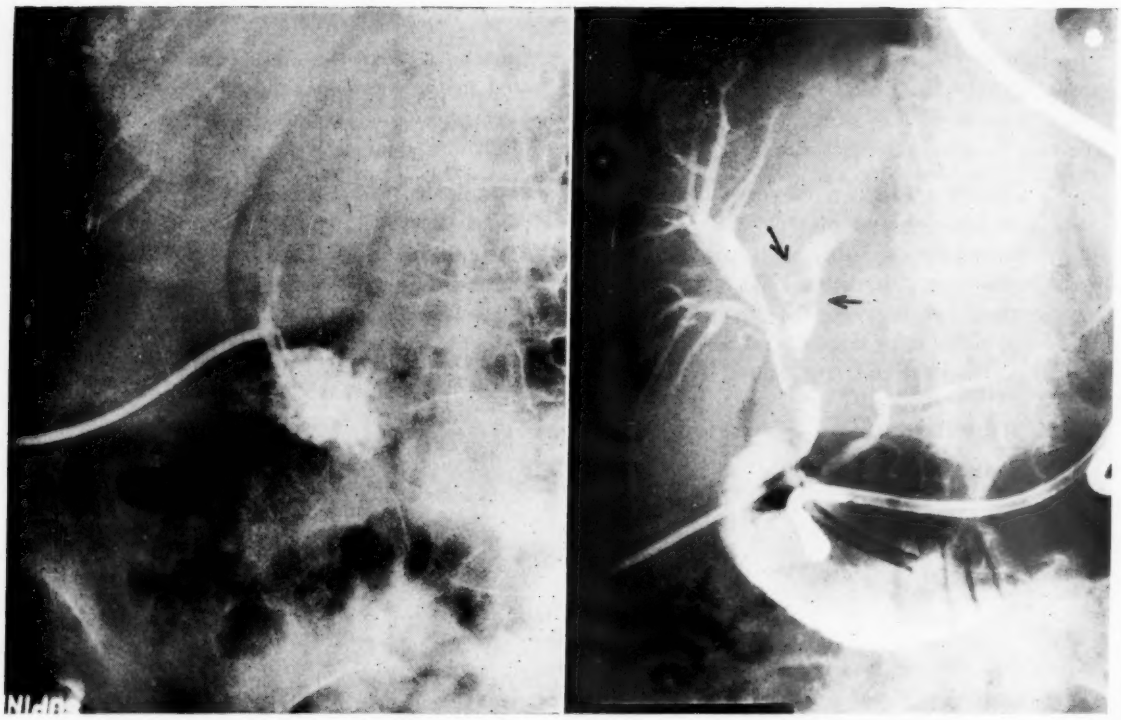


Fig. 1.—Abbott-Rawson tube with balloon attached to distal portion. A convenient length of the single lumen portion *A* to *B* is 12 cm. Additional perforations in the portion of the tube confined in the balloon insure prompt introduction and withdrawal of air.

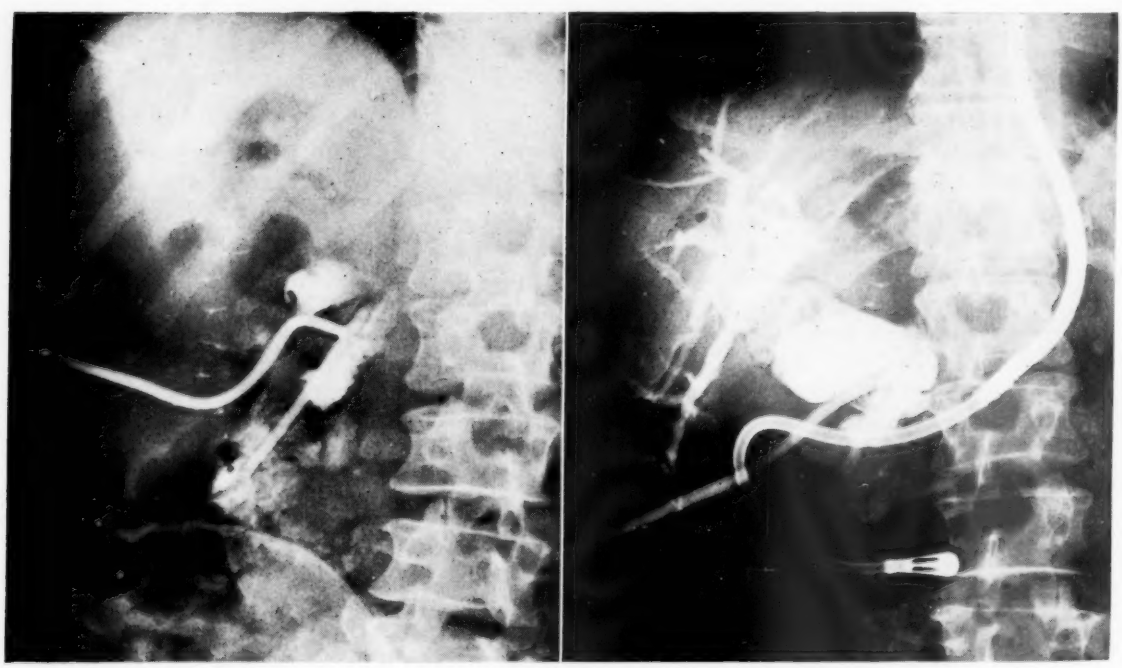
A routine cholangiogram was performed shortly after operation (Fig. 3*A*), as well as seven months later; the upper biliary tract was not visualized on either occasion. A third attempt, using the balloon technique, satisfactorily outlined the common duct and the remainder of the biliary tree (Fig. 3*B*).

CASE 3.—E. W., a 36-year-old Negro housewife, had a cholecystostomy performed at another hospital because of acute pancreatitis. She made an uneventful immediate recovery but four and seven months later experienced attacks of abdominal pain, the last one being accompanied by chills and fever. Two months later she was admitted to the Hospital of the University of Pennsylvania because of prolonged vaginal bleeding. The liver was found to be enlarged and the blood prothrombin concentration greatly diminished. Liver biopsy revealed fibrosis. Duodenal drainage samples contained a small amount of calcium bilirubinate pigment.



A. *B.*

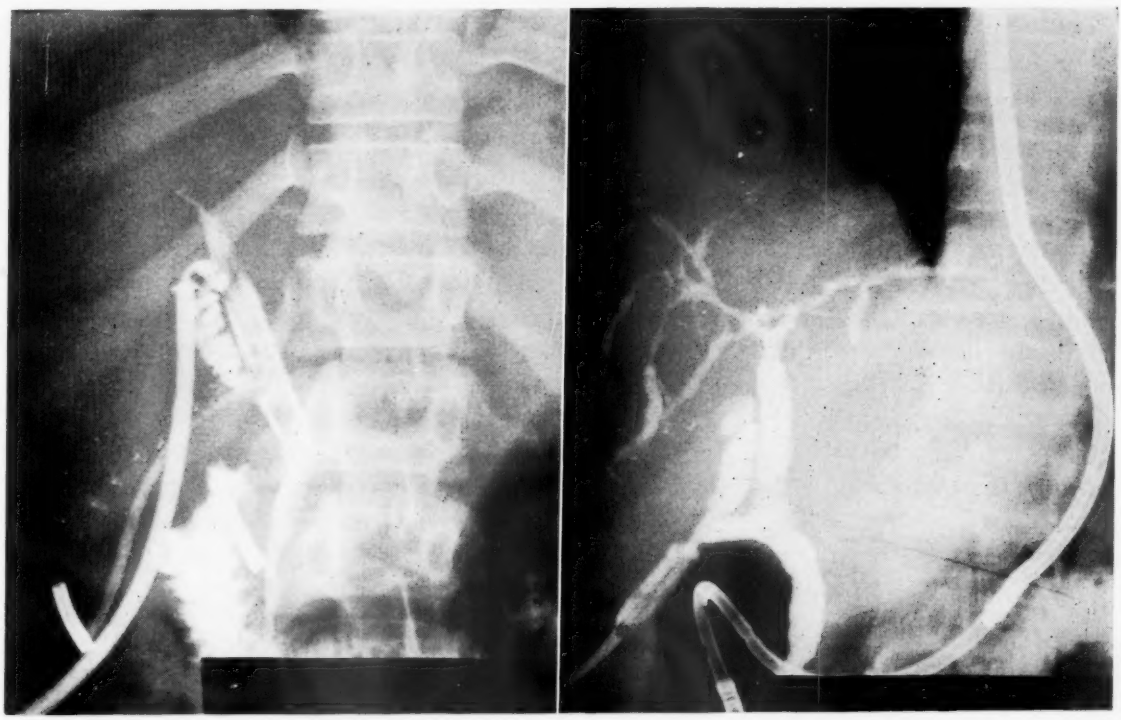
Fig. 2 (Case 1).—*A*, Appearance of cholangiogram as routinely performed. The biliary radicles are not visualized. *B*, Appearance of biliary tree after performing cholangiogram with inflated balloon in duodenum. The main pancreatic duct is visualized. The shadows in the left hepatic duct indicated by arrows are caused by calculi and sediment.



A. *B.*

Fig. 3 (Case 2).—*A*, Appearance of cholangiogram as routinely performed. The biliary radicles are not visualized. *B*, Appearance of cholangiogram performed with balloon inflated in the duodenum. The biliary tree is satisfactorily visualized and contains no obstructing lesions or visible calculi.

Exploratory laparotomy disclosed no lesion or calculus in the common duct; it was found impossible to explore the hepatic ducts. The gall bladder was removed and a T tube inserted into the common duct. A cholangiogram, performed in the usual manner, revealed patent common hepatic and bile ducts, but the dye failed to go beyond the junction of the right and left hepatic ducts (Fig. 4*A*). Subsequently, the duodenum was intubated, the balloon inflated, and the cholangiogram repeated. This time a markedly shrunken and narrowed but unobstructed intrahepatic biliary tree, with dilated terminal radicles, was clearly visualized (Fig. 4*B*). The significance of the appearance of the biliary tree at this time is not fully understood; it is suspected that it is indicative of cholangitis.



A. *B.*

Fig. 4 (Case 3).—*A*, Appearance of cholangiogram as routinely performed. The biliary radicles are not visualized. *B*, Appearance of cholangiogram performed with balloon inflated in the duodenum. The entire biliary tree is visualized. The intrahepatic portion is shrunken and narrowed while the terminal radicles are dilated.

COMMENT

In the cases cited cholangiography as routinely performed failed to yield the desired information due to unsatisfactory visualization of the biliary radicles. Sufficient pressure could not be built up in the biliary tree because the injected dye escaped into the duodenum. Inflation of a balloon in the duodenum prevented the escape of dye downward into the intestine and permitted it to fill the upper part of the biliary tree, thus producing satisfactory visualization.

SUMMARY

1. A procedure is described which permits more adequate visualization of the biliary radicles than does cholangiography as usually performed.

2. It consists of inflating a balloon in the duodenum at the site of entrance of the common duct, thus preventing the injected radiopaque dye from escaping downward into the duodenum and permitting it to fill the upper part of the biliary tree.

3. Three case reports are cited wherein this procedure yielded information not obtained by cholangiography as routinely performed.

REFERENCES

1. Abbott, W. O., and Rawson, A. J.: A Tube for Use in the Postoperative Care of Gastroenterostomy Cases, J. A. M. A. **108**: 1873, 1937.
2. Cotte, M. G.: The Radiological Exploration of the Biliary Tracts After Injection of Lipiodol Following Cholecystostomy and Cholecystectomy, Soc. Nat. de Chir. **55**: 863, 1929.
3. Overholt, R. H., Biliary Tract Visualization With Radiopaque Oils, Surg., Gynec. & Obst. **52**: 92, 1931.

EFFECT OF N-ALLYLNORMORPHINE* ON GASTROINTESTINAL MOTILITY

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INTEREST in the alkaloid, n-allylnormorphine, has arisen because of the ability it apparently has to antagonize the effect of morphine. The published reports have been chiefly concerned with the effects of the drug upon the central nervous system.[2-6] The present studies were conducted to determine the effect of n-allylnormorphine upon the motility of the gastrointestinal tract.

METHODS AND MATERIALS

Three adult male patients from the surgical wards of Wadsworth General Hospital, Veterans Administration Center, Los Angeles, were studied. These patients, whose ages were 43, 55, and 71 years, were studied after they had fasted for at least eight hours. Intraluminal balloons were inserted under fluoroscopic control into various portions of the gastrointestinal tract. Motility was recorded by means of a multichannel oscillographic recorder.[1] In two cases, gastrointestinal activity was stimulated by the injection of morphine sulfate prior to the administration of n-allylnormorphine. In the other patient, the gastrointestinal tract was not stimulated before the administration of n-allylnormorphine.

RESULTS

The effect of n-allylnormorphine in the three patients studied is summarized in Table I.

One patient had balloons placed in the lower third of the esophagus, in the proximal portion of the jejunum, and in the sigmoid colon. A marked increase in tonus and contractions of these portions of the intestinal tract followed the intravenous injection of 10 mg. of morphine sulfate. Seventeen minutes later, 5 mg. of n-allylnormorphine was administered intravenously, and the effect of morphine was promptly inhibited (Fig. 1).

The spontaneous motor activity of the stomach, proximal jejunum, and sigmoid in one patient was recorded for a period of 50 minutes, after which 5 mg. of n-allylnormorphine was injected intravenously. A brief period of increased tonus and contractibility followed in the jejunum. Motility of the stomach and colon was promptly inhibited, and the brief period of increased motor activity of the jejunum was followed by a period of depressed motility also (Fig. 2).

In a third patient similar, but less striking, findings were noted (Fig. 3). In this case both morphine and n-allylnormorphine were given subcutaneously.

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*The n-allylnormorphine (Nalline) was supplied by the Medical Division of Merck & Co., Inc., Rahway, N. J.

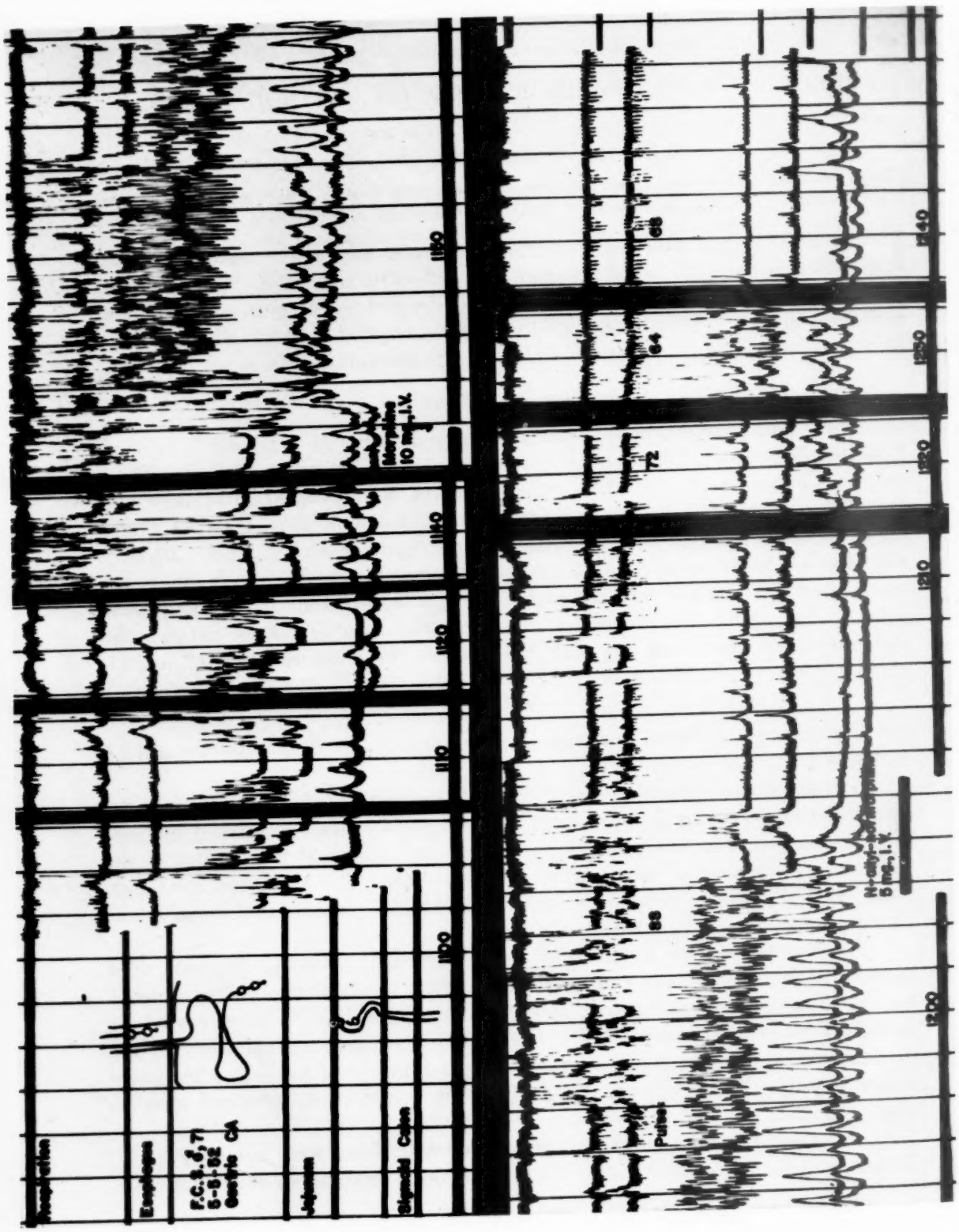

Fig. 1.—Record of motility of esophagus, jejunum, and sigmoid colon. Five milligrams of n-allylnormorphine was injected intravenously thirteen minutes after 10 mg. of morphine had been administered. The spasm induced by morphine was promptly diminished.

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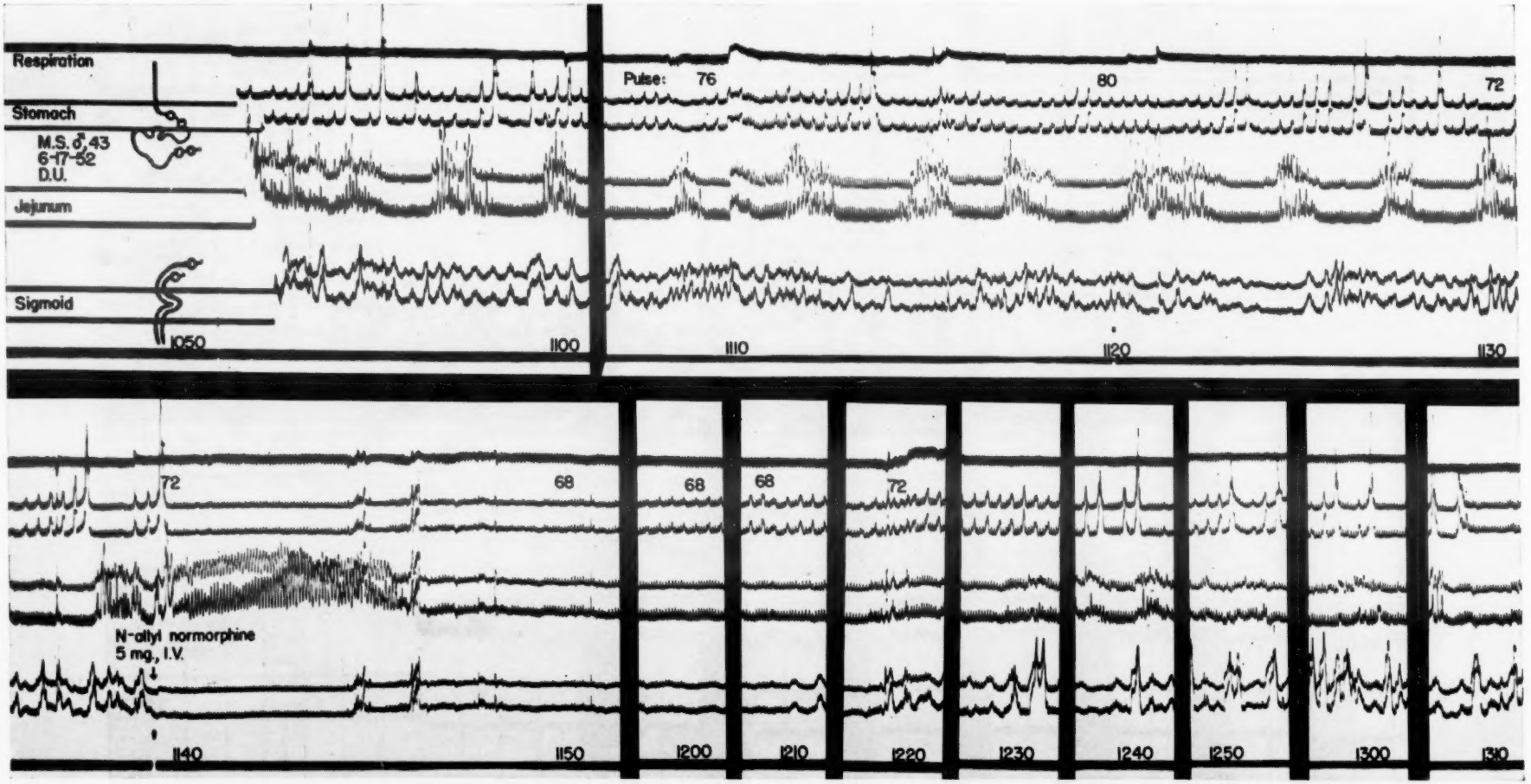
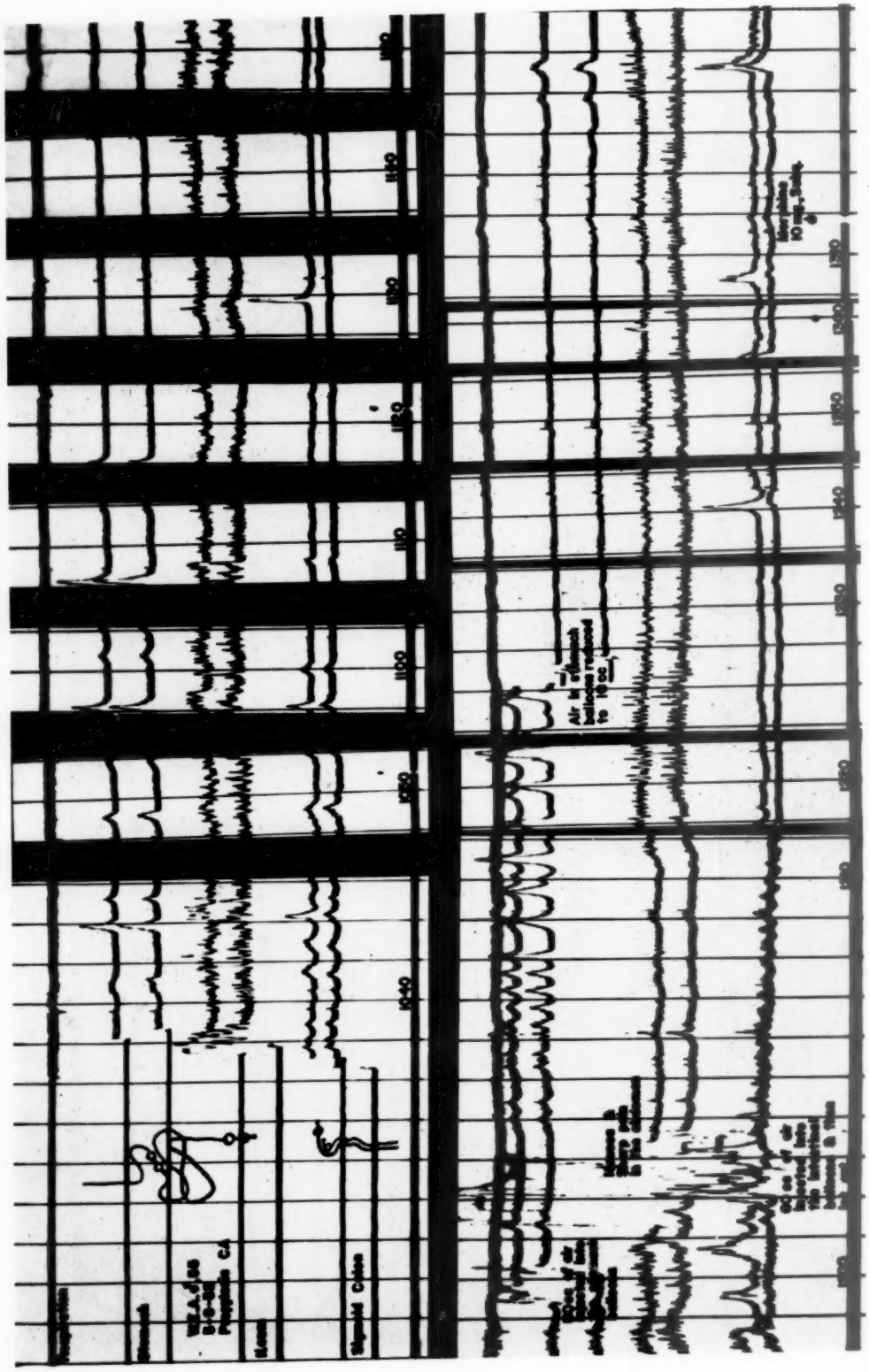


Fig. 2.—This record illustrates the effect of n-allylnormorphine on spontaneous motor activity of the stomach, jejunum, and sigmoid colon in a 43-year-old man.



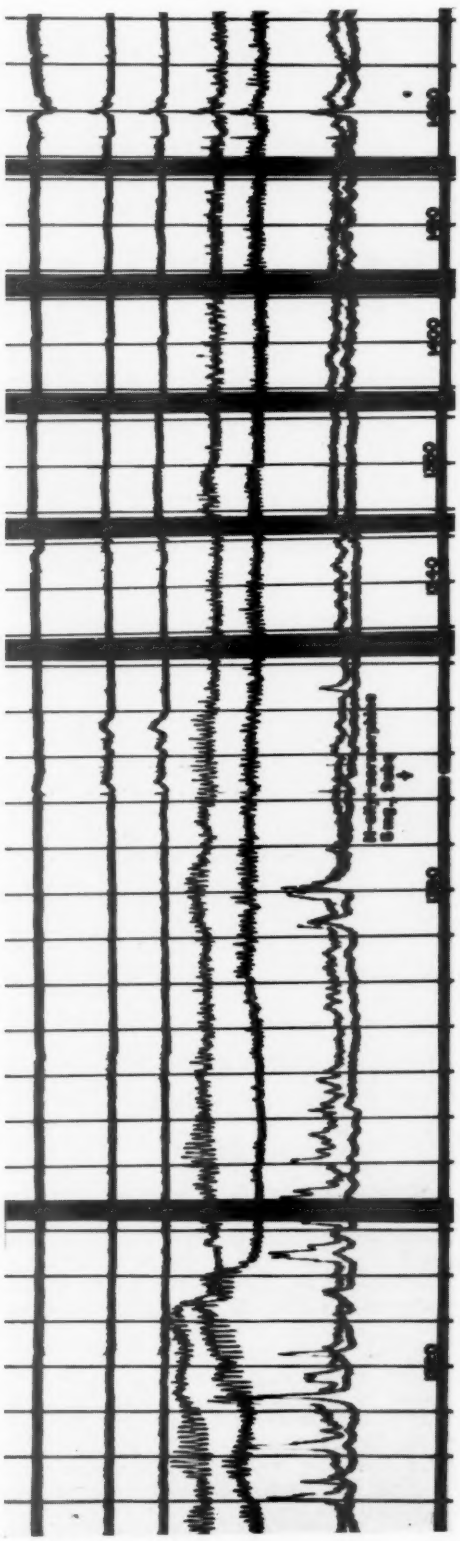


Fig. 3.—Record of motor activity of the stomach, ileum, and sigmoid colon in a 55-year-old man. Ten milligrams of morphine given subcutaneously was used as a stimulant. Five milligrams of n-allylnormorphine was injected subcutaneously twenty-two minutes later. The gastric balloon did not function satisfactorily in this tracing.

TABLE I

SUBJECT	TYPE OF STIMULATION	LEVELS OF GUT INTUBATED	LENGTH OF INHIBITION
1. F. C. S.	Morphine	Esophagus	40 minutes
♂, 71		Jejunum	40 minutes
Gastric carcinoma		Sigmoid colon	20 minutes
2. W. E. A.	Morphine	Stomach	---------*
♂, 55		Ileum	----------
Gastric carcinoma		Sigmoid colon	50 minutes
3. M. S.	Spontaneous	Stomach	30 minutes
♂, 43	Motility	Ileum	60 minutes
Duodenal ulcer		Sigmoid colon	40 minutes

*Inhibitory effect indeterminate.

The effect was not as prompt nor as marked as was the case in the previous patients, and, in addition, the balloon in the stomach was not functioning satisfactorily. It does appear that the n-allylnormorphine depressed the activity of the colon which had been stimulated by the subcutaneous injection of 10 mg. of morphine.

DISCUSSION

From the published reports concerning the action of n-allylnormorphine in antagonizing the respiratory and circulatory depression of morphine and compounds related to morphine, it would appear that the site of action is upon the central nervous system.[2-6] The action of morphine upon the gastrointestinal tract is a direct one, although the mechanism is not clearly understood. It would, therefore, seem that n-allylnormorphine not only antagonizes the effect morphine has on the central nervous system, but also counteracts its peripheral effects at least in the gastrointestinal tract. The response to the intravenous administration of this drug in the absence of stimulation with morphine suggests that, in addition to counteracting the effect of morphine, n-allylnormorphine also exerts an independent effect on the gastrointestinal tract.

SUMMARY

N-allylnormorphine inhibited gastrointestinal motor activity following stimulation by morphine. Spontaneous motility was also diminished. The action was prompt and persisted for from 20 to 60 minutes after injection.

REFERENCES

1. Bachrach, W. H., Brady, M., and Drury, D. R.: The Multiple Simultaneous Recording of Gastrointestinal Functions, Gastroenterology **18**: 609, 1951.
2. Eckenhoff, J. E., Elder, J. D., and King, B. D.: N-Allyl-Normorphine in the Treatment of Morphine or Demerol Narcosis, Am. J. M. Sc. **223**: 191, 1952.
3. Huggins, R. A., Glass, W. G., and Bryan, A. R.: Protective Action of N-Allyl-Normorphine Against Respiratory Depression Produced by Some Compounds Related to Morphine, Proc. Soc. Exper. Biol. & Med. **75**: 540, 1950.
4. Huggins, R. A., Glass, W. G., and Bryan, A. R.: Protective Action of N-Allylnormorphine Against the Respiratory Depression Produced by Some Compounds Related to Morphine, J. Pharmacol. & Exper. Therap. **101**: 19, 1951.
5. Wikler, A., and Carter, R. L.: Effects of Morphine and N-Allyl-Normorphine on Reflexes in Dog and Cat, Federation Proc. **11**: 402, 1952.
6. Zauder, H. L.: Antagonistic Effect of N-Allyl-Normorphine on Morphine Induced Hyperglycemia, Federation Proc. **11**: 405, 1952.

THE SURGICAL SIGNIFICANCE OF THE SUBAREOLAR LYMPH PLEXUS IN CANCER OF THE BREAST

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DESPITE over one-half century of experience with radical mastectomy, local recurrence following this operation continues to represent a serious failure of the procedure. Reported rates of local recurrence vary from 2.2 per cent[1] to 22.8 per cent.[2] An expectancy of 10 per cent local recurrence is about average.[3]

The incidence of local recurrence is influenced by a multitude of variable factors such as how old the patient is, whether metastasis to regional nodes has occurred, and whether there is practiced strict compliance with arbitrary criteria of inoperability. Perfection can be attained by selection. Therefore surgeons have been reluctant to accept conclusions in support of a technical aspect of radical mastectomy based only on statistics. For example, there is no uniformity of opinion as to the value of routine skin grafting.[4]

In such a dilemma the solution must be sought in the basic facts of anatomy and physiology. This is being done by Wangensteen,[5] Sampson Handley,[6] and Urban,[7] who are investigating by surgical extirpation supraclavicular and internal mammary node metatstasis. In the presence of unrecognized involvement of these nodes, the ordinary radical mastectomy is, of course, inadequate.

In addition, we have been investigating the channels of lymph flow of the breast by dye injection studies in an effort to learn how technical improvement in radical mastectomy can be accomplished.

One phase of this study has already brought forth information which, though not new, is important and has not been emphasized in surgical literature.

METHOD

The breasts of patients who were to undergo radical mastectomy were injected with 2 c.c. of a 0.5 per cent solution of Evans blue dye (T 1824).* This dye was selected on the advice of Dr. Philip McMaster of the Rockefeller Institute for Medical Research because of its high molecular weight. This characteristic of the dye made it especially suitable for dynamic lymphatic studies. Its ready availability in sterile ampules and proved nontoxity from blood volume studies was also a valuable feature of this dye.

All quadrants of the breast were injected. The injections were made into the normal parenchymatous breast tissue away from the tumor site. Time of injection varied from 15 minutes to 7 days preoperatively, with most injections given 24 hours preoperatively. A total of 20 breasts were injected for this particular study. Immediately following removal, the breast was carefully dissected along all visible ramifications of the dye.

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*Provided through the courtesy of Wm. R. Warner & Co., Inc., New York, N. Y.

THE LYMPHATIC SYSTEM OF THE MAMMARY GLAND

The anatomy of the lymphatic vessels draining the parenchyma and the overlying skin of the breast is rather intricate and poorly understood. We are indebted to Rouvier for correlation of the magnificent work of the earlier anatomists, in particular such men as Sappey, Mornard, Bartels, Oelsner and others who made such careful and detailed studies of the lymphatic vessels of the breast and the routes of drainage to regional lymph nodes.[8] In order to better understand this somewhat complex lymphatic system, Figs. 1 through 5 have been prepared. For the sake of simplicity and clearer understanding, the lymphatics of the breast are described under two separate headings: Cutaneous Lymphatics and Parenchymal Lymphatics.

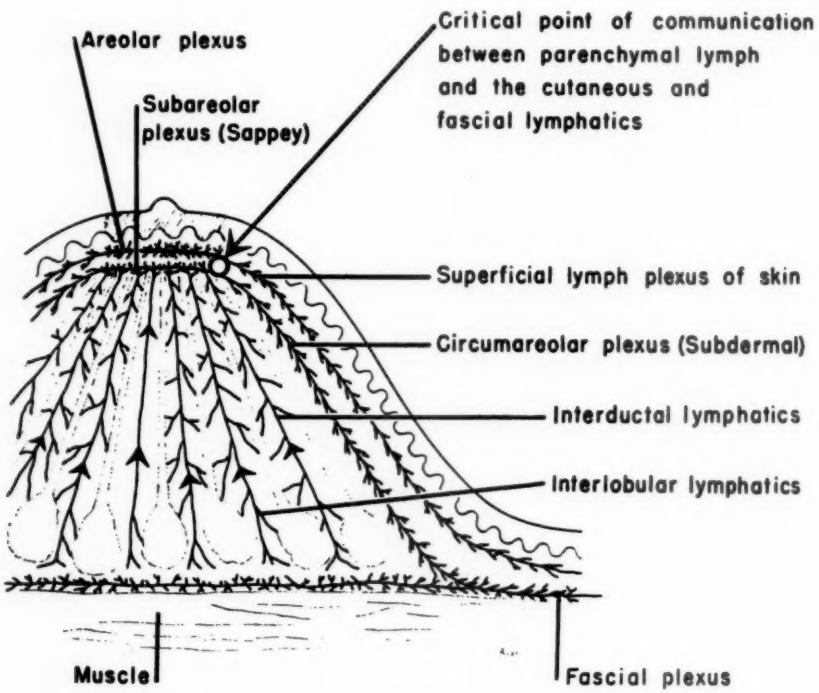

Fig. 1.

Cutaneous Lymphatics.—The superficial lymph plexus of the skin of the breast (see Fig. 1) which lies just deep to the epidermis and within the dermis can be divided into two levels. The first and more superficial network consists of a dense plexus in the region of the nipple and the areola and is termed the areolar plexus. It is continuous at its periphery with the less dense superficial lymph plexus (papillary lymph plexus of the skin) which is identical with that present throughout the remainder of the body. On a deeper plane and situated in the subdermal tissues is a second plexus of rich lymphatic vessels. This plexus is much more dense in the region corresponding to the undersurface of the nipple and areola where it is known as the subareolar lymphatic plexus (Sappey) and assumes paramount importance as will be discussed later. This subdermic plexus becomes less dense at the outer circumference of the areola and is here known as the circumareolar lymphatic plexus. This plexus merges with the superficial fascial plexus at the periphery of the breast proper. This arrangement of the cutaneous lymphatics in the region of the breast is peculiar and unlike the arrangement found elsewhere in the skin of the body. In the mammary region the superficial fascial plexus lies in the retromammary tissue and just superficial to the fascia of the pectoralis major muscle. Elsewhere this plexus is located in the deeper portions of the subcutaneous tissue where it drains the epidermis, the dermis, and the more superficial portions of the subcutaneous

tissue by vertical lymphatic vessels emptying directly into it. There is no subdermal lymphatic plexus corresponding to the subareolar and circumareolar plexus of the mammary region elsewhere in the body.

The cutaneous lymphatics, as the name implies, drain the overlying skin of the breast. The areolar component of this plexus drains the overlying nipple and areola and in turn drains directly down into the rich subareolar lymphatic plexus (Sappey). The cutaneous lymphatics elsewhere over the breast drain directly down into the circumareolar plexus which, as we have seen, merges with the superficial fascial plexus at the periphery of the breast. The circumareolar plexus (see Fig. 2) in turn is drained primarily by what is referred to as the principal cutaneous lymphatic trunk. This trunk, which drains the cutaneous lymphatic network, converges upon the axilla and empties into the external mammary group of nodes, especially the superior nodes of the group. This path also represents the principal means by which the entire anterolateral thoracic wall is drained. There are, in addition, several secondary paths which drain the circumareolar plexus and the anterior thoracic wall: (1) the subclavicular path consisting of one or two lymphatic trunks which pass directly upward into the apical axillary nodes or the subclavicular nodes, (2) the internal mammary lymphatics which drain the skin over the medial portion of the breast and the anterior thoracic wall and accompany the perforating branches of the internal mammary vessels to empty into the nodes of the internal mammary chain, (3) the anterolateral lymphatic path demonstrated by Oelsner consisting of collecting trunks which cross the midline and drain into the axillary nodes of the opposite side. It explains the method by which contralateral axillary nodes may be involved in a cancer of the opposite breast.

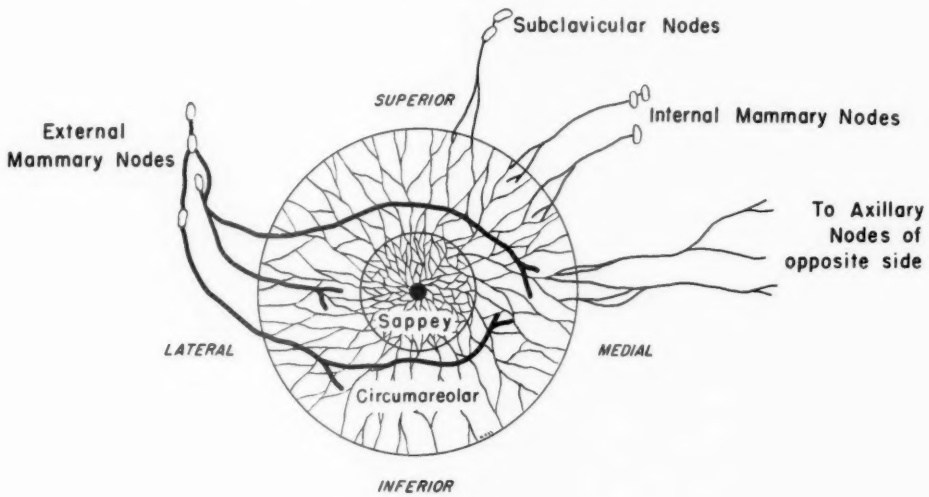

Fig. 2.—Cutaneous lymph drainage of breast.

There is a second method by which a cancer may spread from one mammary region to the other, that is, by way of the cutaneous network of both mammary regions which is continuous across the midline.

Parenchymal Lymphatics.—This system is best understood when considered under the following two headings: (1) *The collecting lymphatics* begin in the terminal interlobular tissues and become interductal lymphatics and finally empty into the subareolar plexus. (2) The *drainage lymphatics* provide the routes by which the lymph leaves the breast proper. The latter consists of (a) the principal axillary path and (b) the accessory pathways.

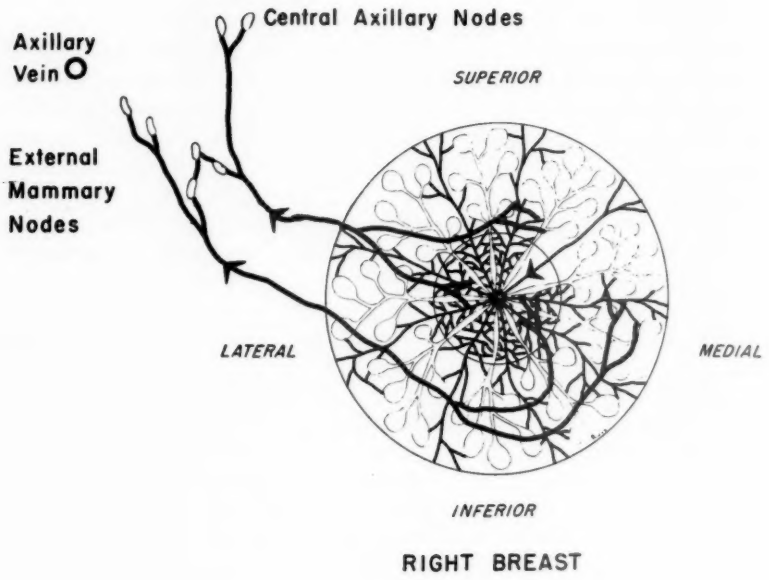

Fig. 3.—Principal axillary path (Sappey) of breast.

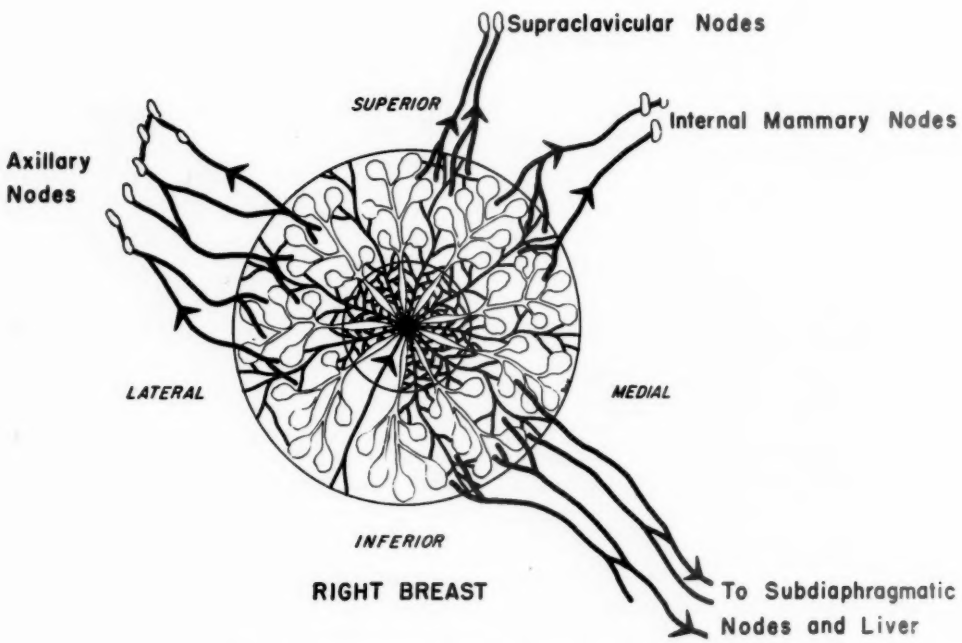

Fig. 4.—Accessory lymphatic paths of breast.

The principal axillary path (see Fig. 3) is the most important route by which lymph leaves the breast toward the regional nodes. Almost all the lymph drainage of the breast is via this path which drains the subareolar plexus and terminates in the external mammary chain of axillary nodes. It consists of two main lymph trunks, one arising from the inner part and one from the outer part of the subareolar plexus. Each trunk receives a principal tributary which in the case of the lateral trunk comes directly from the superior part of the mammary gland and joins it, while that from the inferior part of the mammary gland joins the medial trunk. Both trunks terminate in the nodes of the external mammary chain. Others may run directly to the nodes along the axillary vein or to the central group of axillary nodes.

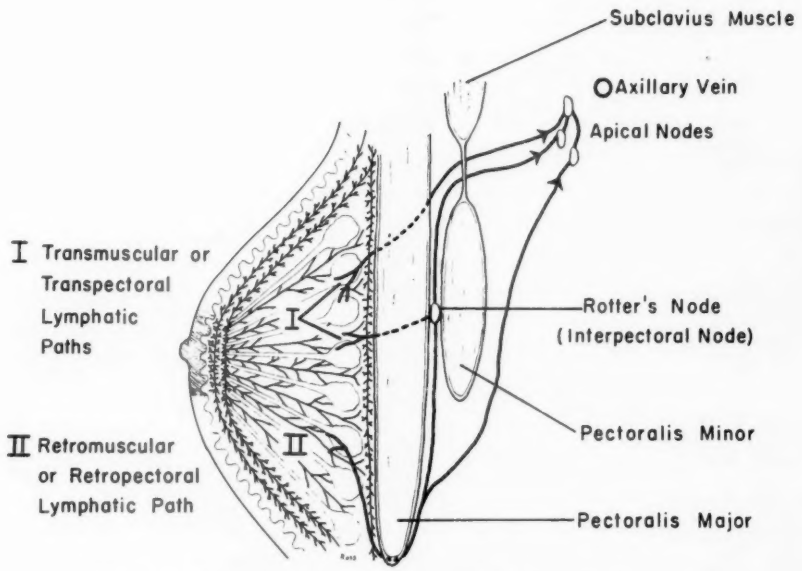

Fig. 5.—Additional accessory lymphatic paths of breast.

The accessory lymphatic paths of the breast (see Fig. 4) represent a minor lymph drainage system carrying only a small amount of lymph from the various segments of the breast into the adjacent lymph nodes. They include: (1) vessels which drain the outer half of the breast directly into the axillary nodes, (2) vessels which may drain the supramedial portions of the mammary gland ascending either behind the pectoralis major muscles or between the two pectoral muscles, beneath the clavicle, to end in the supraclavicular nodes, (3) vessels which drain the medial portion of the breast, accompanying the anterior perforating branches of the internal mammary blood vessels, traversing the pectoralis major and intercostal muscles; to the internal mammary nodes, (4) vessels which pass down from the breast and communicate with the subperitoneal lymph plexus through the upper thin part of the linea alba along the triangular ligament to the liver, (5) vessels (see Fig. 5) designated as the transmuscular or transpectoral lymphatics which drain some of the upper portion of the breast and transverse the pectoralis major muscle and the costocoracoid membrane to end directly in the apical group of axillary nodes, or indirectly via Rotter's node situated between the two pectoral muscles, (6) vessels of the retromuscular or retropectoral lymphatic path (see Fig. 5), consisting of one or two vessels which wind around the inferior border of the pectoralis major muscle and pass either between the two pectoral muscles or behind the pectoralis minor to the apical or subclavicular lymph nodes. One or two interpectoral nodes may interrupt the lymphatic vessel en route to the apical nodes.

THE SUBAREOLAR LYMPH PLEXUS

The centripetal flow of lymph along the interlobular and interductal lymphatics from the parenchyma toward the areola is shown in Fig. 1. Here cir-

cumferential flow in the subareolar plexus makes possible pooling, and mixture, of lymph from all parts of the breast before it passes on to the axillary lymphatics.

The subareolar plexus communicates with two adjacent separate lymph streams. One is immediately superficial to it, the areolar plexus which is a direct continuation of the superficial cutaneous lymph plexus. The other is lateral, the circumareolar lymphatics, which blend directly with the important fascial lymphatic system. Thus there is a critical point at which there is easy communication between all of the parenchymal breast lymph, and the lymph channels of the skin and fascial plexus. This type of lymph flow is illustrated in Fig. 6 in which dye staining of the skin occurred 2 cm. peripheral to the areolar margin on the opposite side of the breast from the site of the dye injection. These phenomena, i.e., centripetal flow of the dye and subareolar and circumareolar lymph plexus staining, and overlying skin staining, were observed from injections made in all quadrants of the breast. The stained lymphatics were found to approach closer to the undersurface of the skin as the areolar margin was approached. It was found relatively easy to dissect a skin flap which remained completely superficial to dye-stained lymphatics at the periphery of the breast. However, as the areolar margin was approached the thinnest skin flaps that could be dissected were frequently cut through dye-stained lymphatics. Fig. 7 shows the undersurface of the skin of a radical mastectomy specimen and demonstrates the pooling of dye which has occurred in the subareolar and areolar plexus with an unstained interval of space between the injection site and the subareolar area.

Thus there are four significant aspects of this type of lymphatic flow: (a) centripetal flow from the breast parenchyma with resulting (b) subareolar pooling and concentration, (c) close proximity of the subareolar lymphatics plexus to the skin, and (d) communication of the parenchymal and cutaneous lymph stream in the subareolar area (see Fig. 1).

COMMENT

Surgical textbooks and articles on the technique of radical mastectomy all emphasize the necessity for wide removal of the skin of the breast in the region of the tumor. However, no point is made of the necessity for wide clearance of the areola. For a centrally located lesion this is automatically accomplished by clearing the tumor by a wide margin. However, in a peripherally placed lesion, especially if large, there may be the temptation to fashion skin flaps which approach the areola on one margin.

If it can be assumed that cancer cells can follow the same lymphatic pathways as the dye, it would seem that the communication of the parenchymal lymph with the cutaneous network via the subareolar plexus would explain the frequent and often bizarre intracutaneous recurrences seen either early or late following radical mastectomy. Furthermore, it would seem that the areola must be cleared by as wide a margin as possible in all directions. Two centimeters was shown to be the absolute minimum margin necessary. Moreover, if one accepts the principle that transection of lymph channels between the primary lesion

Fig. 6.

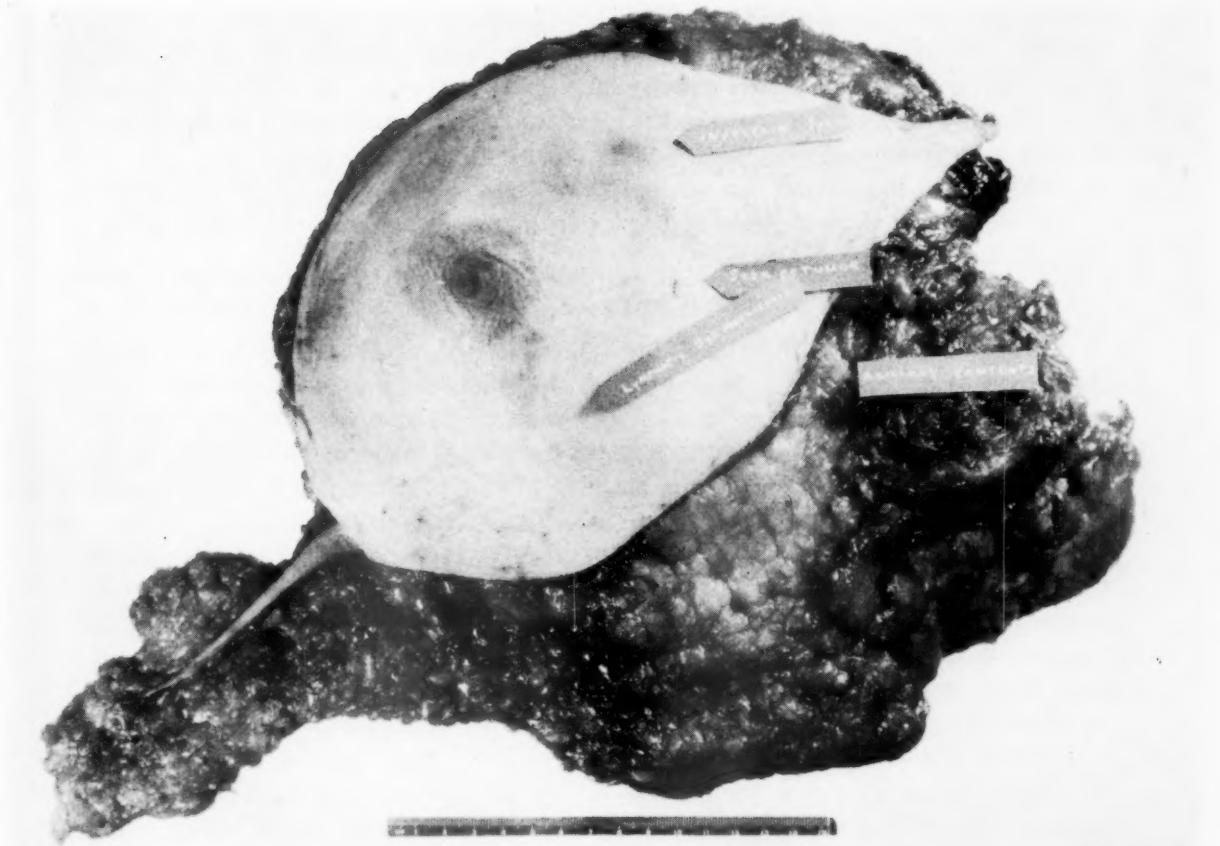

Fig. 7.

Fig. 6.—Stained skin overlying stained subareolar and circumareolar plexus extending 2 cm. peripheral to the areolar margin on the opposite side of the breast from site of dye injection.

Fig. 7.—Undersurface of skin of breast showing pooling of dye in subareolar and areolar plexus with unstained interval of space between injection site and subareolar area.

and the regional lymph nodes must be avoided wherever possible in cancer surgery, complete excision of the skin of the breast must be considered the ideal method. However, many surgeons feel that wide skin excision and thin peripheral breast skin flaps is equally effective. Certainly in this study it was found that at the periphery of the breast it was easy to dissect in a plane superficial to grossly stained lymphatics.

This study emphasizes the concept that the location of the lesion is a factor no less important than the size of the lesion in determining whether skin grafting will be required.

SUMMARY AND CONCLUSIONS

1. The anatomic pathways of the lymph drainage of the breast are being studied in order to improve the cure rate of operable cancer of the breast.

2. These studies have been made by the injection of Evans blue dye (T 1824) into the various quadrants of the normal breast parenchyma prior to radical mastectomy. The staining pattern of the specimen has indicated the direction and channels of lymph flow.

3. A constant and characteristic pattern of lymph flow of the breast is the centripetal direction of flow toward the areola. Drainage of the parenchymal areas is via the interlobular and interductal lymphatics centrally to the subareolar plexus where circumferential flow and pooling occurs before the outflow to the axilla. The subareolar area is therefore a critical region where communication between the parenchymal lymph and the cutaneous lymphatics and the fascial plexus occurs.

4. These facts suggest the mechanism by which skin recurrences evolve and indicate the necessity for wide surgical clearance of the areola area. Skin grafting must be seriously considered in those peripheral lesions where primary closure is not compatible with wide clearance of the areolar area.

REFERENCES

1. Rodman, J. S.: Skin Removal in Radical Amputation, Ann. Surg. 118: 694, 1943.
2. Haagensen, C. I., and Stout, H. P.: Carcinoma of the Breast, Criteria of Operability, Ann. Surg. 118: 1032, 1943.
3. Adair, Frank E., and Grant, Roald N.: Survey of Technical Aspects of Radical Mastectomy. To be published.
4. Conway, Herbert, and Neumann, Charles G.: Evaluation of Skin Grafting in the Technique of Radical Mastectomy in Relation to Local Recurrence, Surg., Gynec. & Obst. 88: 45-49, 1949.
5. Wangensteen, Owen H.: Discussion of Paper by Taylor and Wallace, Ann. Surg. 132: 839, 1951.
6. Handley, R. S., and Thackray, A. C.: Invasion of the Internal Mammary Lymph Glands in Carcinoma of the Breast, Brit. J. Cancer 1: 15-20, 1947.
7. Urban, Jerome A.: Radical Excision of the Chest Wall for Mammary Cancer, Cancer 4: 1263-1285, 1951.
8. Rouvier, C. H.: Anatomie des Lymphatiques de l'Homme, Paris, 1932, Masson & Cie. Translated by Tobias, M. J.: Anatomy of the Human Lymphatic System, Ann Arbor, Mich., 1938, Edwards Brothers, Inc.

THE RELATIONSHIP OF BLEEDING AND CLOTTING TIMES TO MASSIVE TRANSFUSIONS OF CITRATED BLOOD

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THERE are many reports concerning the effects of various agents on bleeding during operative procedures. However, there seem to be no reports in the literature concerning the effect of anticoagulant agents used in stored blood.

This lack of information posed no problem until relatively recent advances in anesthesia made possible more complicated and prolonged operations. The use of massive transfusions, occasionally amounting to total replacement of the blood volume, has made surgeons in general and thoracic surgeons in particular wonder if the steady oozing noticed toward the end of prolonged bloody operations could be related to the citrate in transfused blood.

METHOD

All the patients used in this study underwent major thoracic operations, such as pneumonectomy, lobectomy, or segmental resection. Most of them had tuberculosis and were poor risks.

With one exception, ether was the anesthetic agent, used with an endotracheal, circle absorption, assisted respiration technique. Induction and intubation were accomplished with either a nitrous oxide, ether sequence, or cyclopropane. The one patient who received Pentothal Sodium and D-tubocurarine for induction and intubation (thoracoabdominal esophageal resection) was maintained on cyclopropane. Premedication was consistently pentobarbital, morphine, and atropine.

The median age of the patients was 46 years with extremes of 25 and 72 years.

The bleeding time was taken with a scalpel blade secured in a cork. The wound was blotted continuously with a sponge until the bleeding stopped. The clotting time was taken by drawing a needle through a drop of blood on a glass slide until a fibrin strand was noticed clinging to the needle. An attempt was made to take bleeding and clotting times once an hour. Difficulties with the operative procedure or anesthesia sometimes prevented this.

The blood used in this study contained 120 c.c. of acid citrate dextrose solution. This amount contains 1.58 Gm. of sodium citrate, 0.58 Gm. of citric acid, and 1.76 Gm. of dextrose.

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TABLE I. COAGULATION AND BLEEDING TIMES IN RELATION TO MASSIVE TRANSFUSIONS

NAME	AGE	SEX	RACE	OPERATION	COAGULATION TIME (IN MINUTES)	BLEEDING TIME (IN MINUTES)	TIME	BLOOD (IN C.C.)
D. B.	51	M	White	Right pneumonectomy	4	—	8:20	0
					3		9:20	0
					2½		10:20	600
					2		11:20	3,400
					2		12:35	5,400
M. C.	44	M	Yellow	Right pneumonectomy	3	—	4 hours	5,400
H. J.	53	M	White	Right pneumonectomy	3	—	8:45	0
					2½		9:45	350
					2		11:45	1,800
					2		12:45	3,000
S. L.	29	F	White	Left upper lobectomy	4	—	8:15	0
					4		8:40	0
					4		9:35	250
					3½		10:45	1,200
					4		1:25	2,900
D. B.	35	F	Negro	Right pneumonectomy	4	3	8:00	0
					4	1	9:00	0
					4½	1½	10:00	1,200
					5½	1½	11:00	2,100
					5	1½	12:00	3,300
					5½	2	1:00	3,600
					4½	1½	2:00	4,200
J. B.	42	M	White	Right upper lobectomy and removal of apex of right lower lobe	4	2	9:00	100
					4½	1½	10:00	900
					5	1½	11:00	2,100
					4½	1½	12:00	3,000
					4½	1½	1:00	3,600
					4	2	3:00	4,200
V. R.	25	F	Negro	Left lower lobectomy	6	1	7:45	0
					6	1	8:45	0
					6½	1	9:45	400
					6½	1½	10:45	1,100
					7	2	11:45	1,700
					6	3	12:45	2,600
					6½	3	1:45	3,600
A. W.	72	M	White	Right pneumonectomy	4½	1	8:45	0
					4	1	9:45	400
					4½	1	10:45	1,000
					4	1	12:45	4,000
H. M.	57	F	White	Left upper lobectomy	3½	1	9:00	0
					4½	1½	10:00	200
					3	1	11:00	2,000
					4½	2	1:00	2,400
					4	2½	2:00	3,000
J. B.	26	M	White	Left upper lobectomy	3½	—	11:45	0
					4	—	12:45	0
					4	1	1:45	400
					5	1	2:45	600
					4	1½	3:45	850
					3½	1	5:15	3,300
T. D.	39	M	White	Right upper lobectomy	3	1	7:45	0
					4	½	9:15	0
					5	1½	10:15	700
					3	2	11:15	1,600
					3	1	1:05	2,500

TABLE I. CONT'D

M. M.	50	F	White	Right pneumonectomy	4	1	8:30	0
					3½	1	11:45	3,000
N. C.	60	F	White	Thoracoabdominal, esophageal resection	2	1	8:40	0
					4½	1	9:40	100
					3½	1	10:40	500
					3	1	11:40	800
					3½	1	12:40	1,000
					4	1	2:40	1,500
					3	1	3:40	2,000
					4	1	6:30	3,000
R. C.	53	F	White	Right upper lobectomy	5½	3	1:15	0
					4	4	3:00	3,400 (2,400 in ½ hour)
					5	4	4:30	3,800
W. N.	59	M	White	Biopsy of right mediastinal node	2½	—	9:20	0
					2		10:20	600
					2½		11:15	2,400
					2		12:15	3,000

RESULTS

Fifteen patients comprise this series. They all received at least 2,900 c.c. of blood with a median amount of 3,620 c.c. and a maximum of 5,000 c.c. As seen in Table I, the operations were all prolonged. In no case was the bleeding or clotting markedly changed by the large transfusions.

Blood oozed continuously throughout one of the operations. Although the patient's (V. R.) clotting time was somewhat longer than average, there was no change during operation. Subsequently it was found that her prothrombin time was 50 per cent.

We feel that the fifteen consecutive consistent results offer reasonable statistical support for our conclusions.

DISCUSSION

Ivy[1] in 1943 found that massive transfusions of citrated blood apparently were toxic because of the citrate. This experiment performed on dogs did not agree with clinical experience. The discrepancy was not surprising, however, as Neuhof and Hirshfeld[2] estimated that it would be necessary to give 2 to 3 L. of citrated blood in fifteen minutes to produce toxic symptoms. They approached this limit; however, clinically such a drastic measure is hardly ever necessary. In this series, one patient (R. C.) received 2,400 c.c. of citrated blood in thirty minutes when control of the right pulmonary artery was temporarily lost. This particular patient was a small, emaciated woman who probably weighed no more than 90 pounds. She received 0.15 Gm. of sodium citrate per kilogram in thirty minutes with no effect on bleeding or clotting time.

Adams and associates[3] described the symptoms of toxicity in anesthetized animals as a rapid fall in blood pressure, some irregularity of respiration, and very dark blood. No mention is made of increased bleeding and clotting times.

The same author suggests that 4 Gm. of calcium gluconate be given to prevent toxicity in a dog that weighs from 7 to 14 kilograms and has had 60 to 100 per cent of its blood volume replaced with citrated blood.

We had intended to use calcium chloride or calcium gluconate if a hemorrhagic tendency was produced. We felt there was a good possibility that such a tendency would be found because every bottle of citrated blood has some excess of citrate, the excess varying with the amount of blood in the bottle. The average 500 c.c. bottle has enough citrate to maintain 650 c.c. of blood in the liquid state.

There was no increase in bleeding and clotting times or other gross evidence of citrate toxicity under the conditions of this experiment. An explanation is offered by Ross,[4] who states that the transfusion of even large amounts of citrated blood does not produce toxicity, not only because the total is less than the toxic dose, but also because a considerable amount is rapidly metabolized.

It is possible that some alteration in bleeding and clotting times might occur in a baby when a portion of blood might contain a disproportionate amount of citrate. However, under the conditions of this experiment on adults, there was no effect on bleeding and clotting times by massive transfusions of citrated blood.

SUMMARY

An attempt was made to establish the relationship of bleeding and clotting times to massive transfusions of citrated blood. Under the conditions of this experiment, massive transfusions of citrated blood had no effect on bleeding and clotting times.

REFERENCES

1. Ivy, A. C., Greengard, H., Stein, J. F., Jr., Grodius, F. S., and Dutton, D. F.: The Effect of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage, Surg., Gynec. & Obst. **76**: 85, 1943.
2. Neuhof, H., and Hirshfeld, S.: Slow Intravenous Administration of Large Doses of Sodium Citrate, New Method for the Control of Bleeding, New York M. J. **113**: 95, 1921.
3. Adams, W. E., Thornton, T. F., Jr., and Allen, J. G.: The Danger and Prevention of Citrate Intoxication in Massive Transfusions of Whole Blood, Ann. Surg. **120**: 656, 1944.
4. Ross, J. F.: Medical Progress; Blood Banks and Blood Transfusions, New England J. Med. **230**: 171, 1944.

INFLUENCE OF PARENTERAL AUREOMYCIN, CHLOROMYCETIN, TERRAMYCIN, AND PROCAINE PENICILLIN ON THE MORTALITY OF EXPERIMENTAL PERITONITIS

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IT IS the purpose of this paper to provide a comparative study of the effects of the newer antibiotics, administered parenterally, on the mortality of experimental peritonitis.

Since the work of earlier investigators, Fauley and associates,[1] Murphy in collaboration with Ravdin and Zintel,[2] Rothenberg and co-workers,[3] and many others, it has been shown that penicillin and streptomycin have definite value in reducing morbidity and mortality in both clinical and experimental peritonitis. With the development of the newer, broad-spectrum antibiotics, Aureomycin, Chloromycetin, and terramycin, it was advisable that these agents be studied.

Using similar experimental technique, considerable work has already been done in evaluating these antibiotics in the treatment of peritonitis when administered by the oral route. Werner and associates[4] have demonstrated the ready absorption from the gastrointestinal tract and have measured the concentrations of these agents in the blood serum and other body fluids, thus providing a basis for determination of therapeutic dosage levels.

Favorable clinical results in treatment of acute peritonitis with Aureomycin have been reported by Wright and co-workers,[5] who found mortality reduced by 50 per cent over that when penicillin and streptomycin were the agents used. In treating experimental peritonitis in the dog, Schweinburg and associates[6] have reported survival rates as high as 75 per cent, using Aureomycin orally both pre- and postoperatively. In a more recent study of experimental peritonitis in dogs,[7] this same group of investigators, using Aureomycin administered intravenously, reported an over-all survival rate of only 12.5 per cent, a marked difference from the results produced by the oral route of administration. In similar studies by Yeager and his group,[8-11] survival rates of as high as 90 to 100 per cent have been reported with the use of oral Aureomycin and terramycin in experimental peritonitis. Pulaski,[12] experimenting on rats, found the highest survival rates to prevail in rats treated with terramycin and Aureomycin, using the intravenous and intramuscular routes. With a few exceptions the previous experiments in

The antibiotics used in this investigation were provided through the generosity of Lederle Laboratories, Parke, Davis & Co., and Chas. Pfizer & Co., Inc.

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this field have been done using the oral route of administration for preoperative preparation as well as therapy.

The greatest number of patients with peritonitis represent surgical emergencies and, therefore, cannot be treated prophylactically. Many of these patients are unable to retain or absorb oral medication. Therefore, the oral route of medication would be impractical once peritonitis had become established.

In clinical trial there still prevails a multiplicity of variable factors influencing survival, such as etiology, individual resistance, duration of the peritonitis prior to therapy, supportive measures (fluids, decompression, whole blood), and others. All of these factors make it difficult to evaluate the role of antibiotic therapy in influencing the mortality rate. Because most patients with peritonitis cannot take oral medication and cannot be given antibiotics prophylactically, and because it is so difficult to evaluate the results of clinical experience in the treatment of peritonitis, it was decided to determine the relative effectiveness of the three newer antibiotics when administered intravenously in controlled experiments on dogs.

In the present study no special preparation was given the animals except for restriction of food for twenty-four hours prior to operation, in order that the experimental conditions might more closely parallel those most frequently seen in the onset of human peritonitis. It was felt that this would provide a satisfactory gauge of the therapeutic effectiveness of the antibiotics under test.

A previous investigation[13] was conducted in this department to study the effectiveness of parenteral penicillin, streptomycin, and sulfonamides. The control mortality percentages from this former study were used as the control figures for the present series because the experimental method in both cases was precisely the same. A group of dogs was treated with parenteral penicillin in an attempt to reproduce results previously obtained in this laboratory. In presenting this paper we are aware that the conclusions are merely suggestive of results that might be expected in the patient and are subject to the usual limitations on interpretation of animal experiments.

EXPERIMENTAL METHODS

As subjects, adult mongrel dogs, both male and female, were used. These were in apparent good health, and varied in weight from 6.8 to 26.8 kilograms, with an average weight of 15.2 kilograms.

The abdominal areas of the dogs were carefully shaved and scrubbed with soap and water and anesthesia was produced with 0.4 c.c. per kilogram of body weight of a 6 per cent solution of Nembutal administered intravenously. Under rigid aseptic precautions the free peritoneal cavity was opened through an upper abdominal midline incision. The appendix was delivered into the wound and the lateral vessels and mesoappendix were divided and ligated. The base of the appendix was ligated at the level of the cecal wall with a single strand of umbilical tape. The tip of the organ was

then grasped with an Allis forceps and the lumen of the appendix opened by a longitudinal incision from the tip to 1 cm. from the tape ligature. An initial bacteriologic culture was taken from the contents. The opened appendix was then placed back in the peritoneal cavity and by means of the Allis forceps at its tip was rotated between the abdominal viscera and the parietal peritoneum in an arc beginning in the right upper quadrant, extending through the left side, and finally ending in the right lower quadrant where the appendix was deposited. The abdominal wall was then closed in two layers with a continuous suture of black silk for the fascia-peritoneal layer, and a similar suture for the skin.

The initial dose of the selected antibiotic was administered before the dog left the operating table. The dogs were placed in individual enclosures and allowed water as soon as they had recovered from anesthesia. Food was offered twenty-four hours after operation. In this investigation, sixty dogs were treated. An arbitrary period of ten days was set as the duration of the experiment. All dogs surviving were sacrificed on the tenth postoperative day and an autopsy was performed. The dogs which died prior to that time also were subjected immediately to autopsy. At autopsy bacteriologic cultures were again taken from the area which appeared most necrotic. This site was most frequently the appendical area.

ANTIBIOTIC THERAPY

The four antibiotics to be tested were given parenterally. Aureomycin, Chloromycetin, and terramycin were administered intravenously, and procaine penicillin was administered intramuscularly. In the first series of fifteen dogs studied, which included ten dogs treated with terramycin and five dogs treated with Chloromycetin, one-half of the daily dose of the antibiotic was administered every twelve hours. In all other instances, the Aureomycin, Chloromycetin, and terramycin were administered intravenously at the rate of one-fourth of the daily dose every six hours.

Aureomycin hydrochloride buffered with sodium glycinate was dissolved in a solution of 5 per cent dextrose in water. Using a dilution of 20 mg. per cubic centimeter, it was given to five dogs on a dosage schedule of 100 mg. per kilogram per day in four equally divided doses. Ten dogs received 30 mg. per kilogram per day in four equally divided doses, the dilution for five dogs in this latter group being 20 mg. per cubic centimeter, and for the remaining five, 10 mg. per cubic centimeter. Ease of administration was the chief advantage of the more dilute solution.

Chloromycetin, prepared as a 50 per cent solution in acetyldimethylamine for intravenous use, was given in dilution of 250 mg. per cubic centimeter. It was administered to five dogs on a dosage schedule of 30 mg. per kilogram per day in two equally divided doses, and ten dogs received 100 mg. per kilogram per day in four equally divided doses.

Terramycin hydrochloride was diluted with 5 per cent dextrose in water. It was given in a concentration of 25 mg. per cubic centimeter to ten dogs on a

dosage schedule of 30 mg. per kilogram per day in two equally divided doses, and in a concentration of 100 mg. per cubic centimeter to ten dogs on a dosage schedule of 100 mg. per kilogram per day in four equally divided doses.

Wycillin, a type of procaine penicillin, was administered intramuscularly to ten dogs on a dosage schedule of 13,000 units per kilogram per day in two equally divided doses. The dilution was 150,000 units per cubic centimeter, dissolved in 5 per cent dextrose in water.

RESULTS

Clinical Course.—Without exception, those animals which survived for longer than ten hours developed the classical signs of an acute, diffuse, fulminating peritonitis with excessive vomiting, marked abdominal distention, and high fever. The dogs that died during the experimental period developed marked dehydration, stupor, sometimes convulsions or tremors, and coma before death.

Several dogs treated with both dosage levels of Aureomycin warrranted special consideration. A detailed study of both groups revealed instances which indicated evidence of possible anaphylactic response to the agent. Of those treated with 100 mg. per kilogram per day, one dog apparently never recovered from anesthesia and died within six hours of operation. This may have been attributable to the anesthetic. However, two other dogs in this group presented more definite evidence of untoward reaction. Both died within five minutes after receiving the fourth postoperative injection of Aureomycin. Immediately following injection these dogs developed hyperpnea, then dyspnea, after which one dog exhibited what appeared to be a decorticate rigidity and the other dog had an episode of gross hematuria just before death. In the group of dogs that received 30 mg. per kilogram per day one dog died immediately after the first dose of Aureomycin and another immediately after the second dose. Both dogs developed a hyperpnea, followed by respirations of Cheyne-Stokes type, and died within a few minutes. From the pattern of events it seems that these cases might well represent examples of anaphylactic reaction to Aureomycin rather than other forms of toxicity.

Mortality.—The primary object of this investigation was the study of mortality, and the survival rates of the various groups of dogs are shown in Table I. The numbers tabulated indicate the number of dogs that died on a specified day. The 27 control dogs (Group I) are those untreated dogs which were reported in a previous experiment.[13] The survival rate in this group was 3.7 per cent. The single surviving dog in the group had developed a fecal fistula which opened on the abdominal wall. Whether the Chloromycetin and terramycin were given every twelve hours or every six hours made no significant difference in survival rate. Of the ten dogs treated with Aureomycin, 30 mg. per kilogram per day (Group II), a survival rate of 37.5 per cent was found. In the group of five dogs treated with Aureomycin, 100 mg. per kilogram per day (Group III), there were no ten-day survivors. In the statistical evaluation two dogs of Group II and one dog of Group III

TABLE I. NUMBER OF DOGS THAT DIED ON A SPECIFIED EXPERIMENTAL DAY AND THE GROUP SURVIVAL RATES UNDER TREATMENT WITH A GIVEN ANTIBIOTIC

	ANTIBIOTIC AND DAILY DOSE (ON KILOGRAM BASIS)							
		AUREOMYCIN		CHLOROMYCETIN		TERRAMYCIN		PROCAINE PENICILLIN
DAY	CONTROLS	30 MG.	100 MG.	30 MG.	100 MG.	30 MG.	100 MG.	13,000 UNITS
1	18	3	4	1	4	7	5	5
2	4			4			2	
3	1					1	3	
4	1				2	1		
5	1				2			2
6	1	1						
7								
8		1						1
9					1			
10					1			
Total dead	26	5	4	5	10	9	10	8
Sacrificed	1	3	0	0	0	1	0	2
Total dogs	27	8	4	5	10	10	10	10
% Survival	3.7	37.5	0	0	0	10	0	20

were excluded because it was felt that in these instances, since death occurred within six hours of operation, peritonitis was not a significant factor. There was also 100 per cent mortality in the two groups of dogs treated with Chloromycetin (Groups IV and V). With terramycin, 30 mg. per kilogram per day (Group VI), a 10 per cent survival rate was achieved, and with a dose of 100 mg. per kilogram per day (Group VII), there was 100 per cent mortality. Those dogs treated with procaine penicillin, 13,000 units per kilogram per day (Group VIII), exhibited a survival rate of 20 per cent. Fig. 1 demonstrates these data in graphic form and indicates the differences observed with the various dosage levels.

TABLE II. THE VARIOUS AGENTS COMPARED AS TO AVERAGE SURVIVAL TIME IN HOURS AND MORTALITY RATE

	ANTIBIOTIC AND EXPERIMENTAL GROUP							
	CONTROLS	AUREOMYCIN		CHLOROMYCETIN		TERRAMYCIN		PROCAINE PENICILLIN
	I	II	III	IV	V	VI	VII	VIII
Total dogs	27	8	4	5	10	10	10	10
Dosage (mg. per kg. per day or units per kg. per day		30	100	30	100	30	100	13,000
Average survival time (hours)	47.7	135	18	35	89.4	51.8	43.2	91.2
% Mortality	97.3	62.5	100	100	100	90	100	80

These same experimental results are analyzed in Table II from the point of view of comparing the various agents and dosage levels with the average survival time in hours. In Group I (controls) an average survival time of 47.7 hours is found. With Aureomycin, 30 mg. per kilogram per day, the highest survival time is achieved, while with the elevated dose of 100 mg. per kilogram per day the lowest time of 18 hours is noted. Chloromycetin, 100 mg. per kilogram per day, and procaine penicillin are found to show 89.4 and 91.2

hours, respectively. Terramycin in both dosages shows little statistically significant difference from the control survival time. Fig. 2 is a bar graph illustrating these patterns in comparison with the mortality rate in each group.

Pathology.—Autopsies were performed on the dogs shortly after death with three considerations in mind: first, whether there was a significant degree of localization; second, whether there was any additional abdominal pathology; and, third, whether there was gross pathology of the heart, lung, kidney, or adrenal.

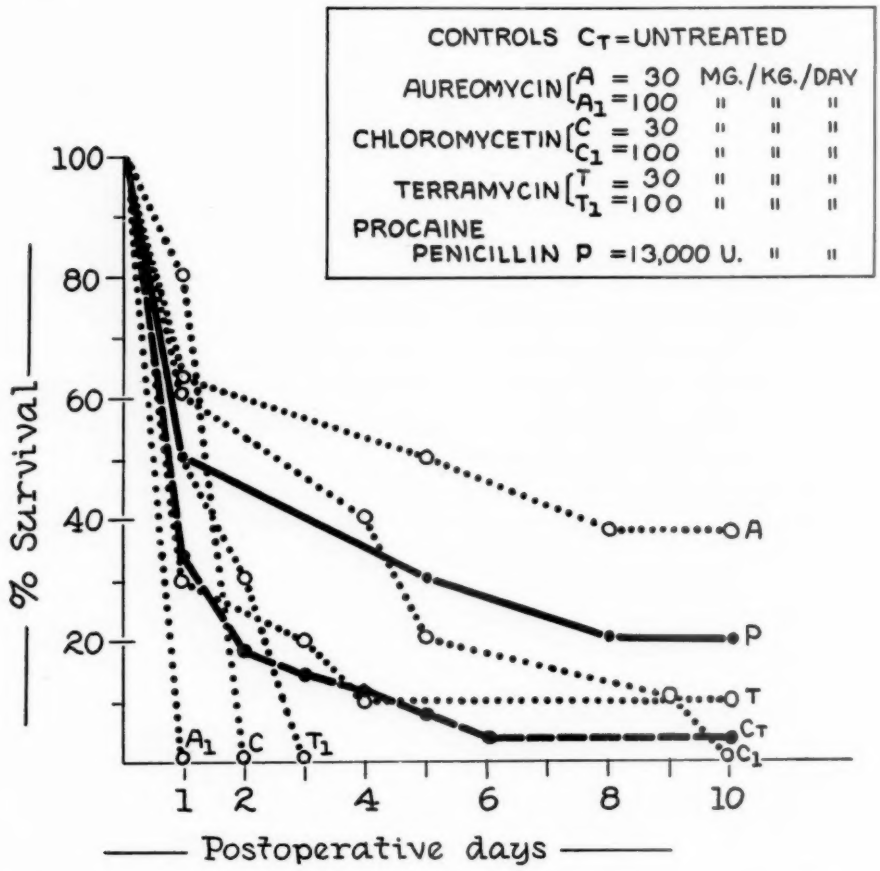

Fig. 1.—Survival rates of dogs treated with broad-spectrum antibiotics and penicillin administered parenterally after production of experimental peritonitis.

Regardless of the agent or dosage level used, all dogs that survived for more than 18 hours but which died prior to the seventh day of the experimental period (75 per cent), showed very little tendency to localization. Diffuse parietal and visceral peritoneal thickening, considerable fibrinous exudate, the formation of moderate amounts of friable adhesions, and relatively large amounts of serosanguineous fluid were the common intraperitoneal findings. No gross abnormality of the kidney or adrenal gland was noted in any dog.

With Aureomycin, the four dogs that died within several minutes of the administration of the dose of antibiotic showed no specific gross pathology to account for the sudden death. There was noted only marked venous congestion of heart, lungs, and kidneys in these dogs. In the three dogs that survived ten days in the 30 mg. per kilogram per day group, there was evidence of good localization of the necrotic appendix with abscess formation.

Three of the dogs treated with Chloromycetin were found to have small hemorrhagic infarcts of the lungs. In the one dog that died on the tenth day of the experimental period was found a completely walled-off appendical abscess, a large quantity of serosanguineous intraperitoneal fluid, and bilateral pleural effusions. In this latter animal the umbilical tape ligature could not be found and there was a direct connection between the bowel lumen and the abscess cavity forming an internal small intestinal fistula.

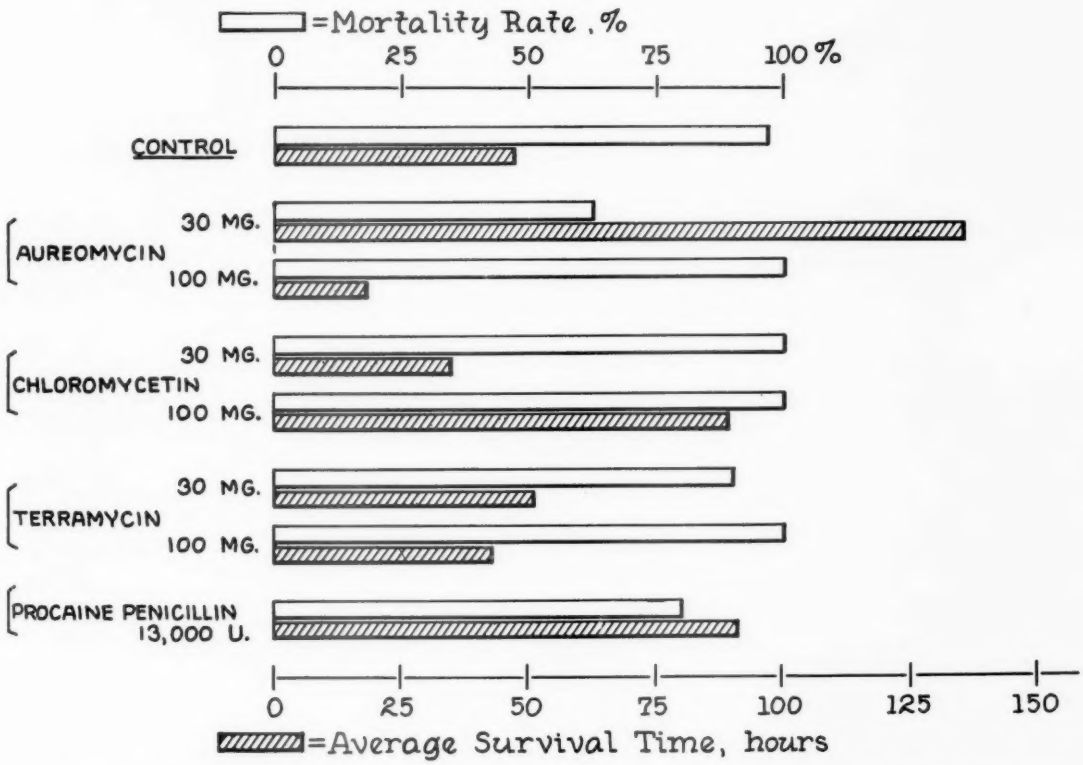

Fig. 2.—Influence of parenteral antibiotics in treatment of experimental peritonitis—comparing mortality rate with average survival time in each group.

Of the dogs treated with terramycin, three were found to have small hemorrhagic lung infarcts and three dogs had dilated flabby hearts. The one surviving animal sacrificed on the tenth day had a well-localized appendical abscess and a small amount of free serous fluid without grossly evident parietal peritoneal involvement.

The autopsy findings on the penicillin-treated dogs did not differ substantially from those found in the case of the other antibiotics. Of the two

dogs that survived the ten-day experimental period, one had a well-localized appendical abscess and very little gross peritoneal reaction. The other animal suffered a wound disruption three days before being sacrificed and apparently had ruptured an appendical abscess externally on the abdominal wall. There was no evidence of fecal fistula in this dog.

Bacteriology.—Determinative bacteriologic studies were made on the control and treated dogs. An analysis of the data confirmed the findings of a previous study.[13]

Death or survival of the dog in any group could not be correlated with a difference in the initial or terminal strains present in the peritoneal cavity.

The strains of bacteria most frequent in initial and terminal cultures were, in order of predominance: Escherichia, Clostridium, Proteus, and Streptococcus (nonhemolytic). There was no significant difference in the frequency of the strains from control or treated dogs either at operation or at autopsy, or between the dogs that lived and those that died.

Bacteria sensitive to the antibiotic used in treatment were frequently found in the terminal cultures.

The strains of Clostridium and Proteus in most instances produced liquefaction of iron gelatin.

DISCUSSION

The specific cause of death following polymicrobic peritonitis due to fecal contamination of the peritoneal cavity is not known. It would seem theoretically likely, however, that the three agents, Aureomycin, Chloromycetin, and terramycin, would be effective against the infectious process since they have a wide bacteriologic spectrum which includes most of the organisms in the intestinal flora. It was hoped that intravenous administration would give an initial rapid high blood level of the antibiotic that might prove the difference between control and overwhelming infection, especially during the first twenty-four hours. These expectations were not borne out by the experimental evidence in the present study.

In practically every group, 50 per cent of the dogs were dead within thirty-six hours of operation. Aureomycin in 30 mg. per kilogram per day doses gave the best over-all ten-day survival rate, and this was only 37.5 per cent. With Aureomycin, 100 mg. per kilogram per day, the mortality rate was 100 per cent. With this agent definite evidence of toxicity was encountered in both dosage ranges. In view of the type of these reactions, it seems most likely that they were anaphylactic responses. The survival time using 100 mg. per kilogram per day was well below the control figure of 47.7 hours, a fact that is quite suggestive of other factors in addition to the peritonitis bearing on the mortality. Evidence of unfavorable reaction to this antibiotic given intravenously in high dosage is reported by Schweinburg and associates[7] in a recent paper.

Chloromycetin in both dosages was ineffective in prolonging survival for the duration of the ten-day experimental period. At the 30 mg. per kilogram

per day level the average survival time in hours was significantly lower than the control figure, while with the higher dosage survival time was almost double that of the control. Why the lower dose should reduce survival time below the control figure is not entirely clear; for, if this were a purely toxic effect, the phenomenon should also be observed with the higher dose. This is not the case, because with the 100 mg. per kilogram per day schedule the agent appears significantly more effective. Perhaps the explanation is that exhibition of this agent in low dosage may result in interference with the immunity responses while not being in sufficient concentration therapeutically to inhibit the organisms.

Terramycin at both dosage levels was singularly ineffective in our experience, there being only one surviving dog of the twenty dogs used. Average survival time in both groups was not significantly different from control survival time.

In this investigation, the dogs treated with procaine penicillin exhibited a 20 per cent survival rate. This is in marked contrast to the 66 per cent survival rate achieved previously when dogs were treated with penicillin-in-beeswax and oil in other similar experiments.[13] The discrepancy is difficult to explain since the experimental method was identical with that used in the previous study. The only difference was in the form of penicillin used. The dosage in both instances was 13,000 units per kilogram per day. Whether more effective blood levels were achieved with the agent used in the former study due to differences in absorption or whether there was a fundamental difference in the penicillin itself has not been determined.

CONCLUSIONS

1. Intravenous Aureomycin in a dosage of 30 mg. per kilogram per day was the most effective agent used in the treatment of experimental peritonitis in the dog.

2. There is evidence to suggest toxicity with the production of an anaphylactic type of response to intravenous Aureomycin at both dosage levels.

3. It is possible that low dosages of Chloromycetin may interfere with immunity responses of the animal when not in adequate concentration to be effectively bacteriostatic.

4. Chloromycetin in higher dosage levels, 100 mg. per kilogram per day, produced significant increase in average survival time. This agent should be investigated using even higher doses.

5. No toxic effects were noted with either Chloromycetin or terramycin.

6. Terramycin was ineffective in our experience at both dosage levels investigated.

7. In this study, procaine penicillin intramuscularly, 13,000 units per kilogram per day, was not as effective as intravenous Aureomycin, 30 mg. per kilogram per day. However, it was more effective than Aureomycin, 100 mg. per day, Chloromycetin, and terramycin. It is noted that we have been unable to reproduce results with procaine penicillin similar to the previous 66

per cent survival rate found with penicillin in beeswax and oil. The reason for this discrepancy has not been finally determined.

REFERENCES

1. Fauley, G. B., Duggan, T. L., Stormont, R. T., and Pfeiffer, C. C.: The Use of Penicillin in the Treatment of Peritonitis—Experimental Study, J.A.M.A. 126: 1132, 1944.
2. Murphy, J. J., Ravdin, R. G., and Zintel, H. A.: The Use of Streptomycin in Experimental Peritonitis, SURGERY 20: 445, 1946.
3. Rothenberg, S., Silvani, H., Spencer, C., Warmer, H., and McCorkle, H. J.: Comparison of the Efficacy of Therapeutic Agents in the Treatment of Experimentally Induced Diffuse Peritonitis of Intestinal Origin, Ann. Surg. 128: 1148, 1948.
4. Werner, C. A., Knght, V., and McDermott, W.: Absorption and Excretion of Terramycin in Humans: Comparison With Aureomycin and Chloramphenicol, Proc. Soc. Exper. Biol. & Med. 74: 261, 1950.
5. Wright, L. T., Schreiber, H., Metzger, W. I., and Parker, J. W.: An Evaluation of Aureomycin Therapy in Peritonitis, Surg., Gynec. & Obst. 92: 661, 1951.
6. Schweinburg, F. B., Rutenburg, A. M., Milrod, S., Glotzer, P., and Fine, J: The Therapeutic Effect of Aureomycin in Experimental Peritonitis in the Dog, Ann. Surg. 133: 208, 1951.
7. Schweinburg, F. B., Glotzer, P., Rutenburg, A. M., and Fine, M. J.: The Therapeutic Effect of Aureomycin in Experimental Peritonitis in the Dog, Ann. Surg. 134: 878, 1951.
8. Yeager, G. H., Ingram, C. H., and Holbrook, W. A.: Comparison of Effectiveness of Newer Antibiotics in Experimental Peritonitis; A Preliminary Report, Ann. Surg. 129: 797, 1949.
9. Yeager, G. H., Byerly, W. L., Jr., and Holbrook, W. A., Jr.: Streptomycin, Aureomycin and Chloromycetin: Experimental and Clinical Comparison, Ann. Surg. 130: 576, 1949.
10. Yeager, G. H., Byerly, W. L., Jr., Holbrook, W. A., Jr., Lynn, W. T., and Barnes, T.: Aureomycin and Chloromycetin in the Treatment of Experimental and Clinical Peritonitis, Bull. School Med. Univ. Maryland 35: 51, 1950.
11. Yeager, G. H., Mansberger, A. R., Jr., Thomas, C. D., Jr., and Barnes, T. G.: Terramycin in Peritonitis: Experimental and Clinical, Ann. New York Acad. Sc. 53: 319, 1950.
12. Pulaski, E. J., Schaffer, J. R., Artz, C. P., and Baker, H. J.: Studies on the Use of Terramycin in Experimental and Clinical Peritonitis, Forum on Fundamental Surg. Prob., Philadelphia, 1951, W. B. Saunders Company, p. 119.
13. Zintel, H. A., Zinsser, H. H., Runyon, W., Jackson, G. L., Nichols, A., Wiley, M. M., and Williams, W. J.: Influence of Antibiotics and Sulfonamides on the Mortality and Bacteria of Experimental Peritonitis, Surg., Gynec. & Obst. 91: 742, 1950.

SURGICAL ASPECTS OF BLASTOMYCOSIS

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THE purpose of this report is to review current trends in the therapy, particularly surgical, of blastomycosis and to present a series of cases in which the disease was treated surgically.

Blastomycosis is a chronic inflammatory disease caused by a yeastlike fungus, *Blastomyces dermatitidis* (Gilchrist and Stokes, 1898). It may affect all organs, particularly skin and lungs. One report[27] on the incidence of the disease in various locations (in a series of twenty-five autopsies) is summarized in Chart I. The route of infection is through the respiratory tract[27] or, rarely, by trauma through the skin.[9] The cutaneous lesion is an indolent papulopustular encrusted patch, enlarging at its periphery. Visceral lesions are either of the chronic granulomatous type or of a more acute exudative, often suppurative, nature. *B. dermatitidis,* with its granular cytoplasm and doubly refractive rim, can usually be found in exudates or biopsies from involved organs. In one series of cases[27] the disease was twenty-nine times as common in men as in women.

Blastomycosis has been treated by high doses of iodides, up to 25 Gm. per day, in conjunction with copper sulfate (locally and systemically), arsenicals, antibiotics, and x-ray.[2, 3, 5, 8, 12-17, 20, 22-24] Desensitization with vaccine before iodide and x-ray therapy has been recommended by several observers.[3, 12, 14, 28] A recent report on the use of stilbamidine has also appeared.[25]

Other observers have reported on the role of surgery in the therapeutic program of blastomycosis. Skin lesions may be treated by excision,[5, 13, 22, 23] curettage[20, 24] (though Hart[13] speculated that this might spread the infection), or electrosurgical destruction in far-advanced cases.[19] Incision and drainage, curettement, and amputation are of value in localized skeletal involvement.[1, 6, 11, 18, 25] A case of posterior mediastinal and spinal canal granuloma was treated by partial excision and x-radiation, and apparently cured, according to Craig and associates.[7] Gaspar[10] noted a case of granulomatous brain involvement, unsuccessfully treated by surgical excision. Cases of laryngeal, prostatic, and uterine blastomycosis, the latter being successfully treated by surgical excision and well after fifteen years, are discussed by a number of observers.[8, 12, 17, 21]

Dr. J. M. Stevenson (Cincinnati) employs a technique of excision and grafting[30] which he used in Cases 1, 3, 4, and 9, and which he will report in detail in a future publication. The essential points of the procedure are: (a) thoroughly cleansing the skin *around* the lesion but no preparation of the lesion

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itself, (b) marking the planned line of incision with methylene blue, (c) suturing several thicknesses of sterile dry gauze over the lesion, the sutures passing through only uninvolved skin around the lesion and only through the dermis and epidermis, (d) excising the lesion, taking care not to cut any of the sutures and to dissect deep to the inflamed tissue without breaking into it, and (e) placing a split or full-thickness graft on the area in the usual manner. Such precautions will prevent contamination of the surrounding skin or the fresh surgical wound by secretions from the involved area.

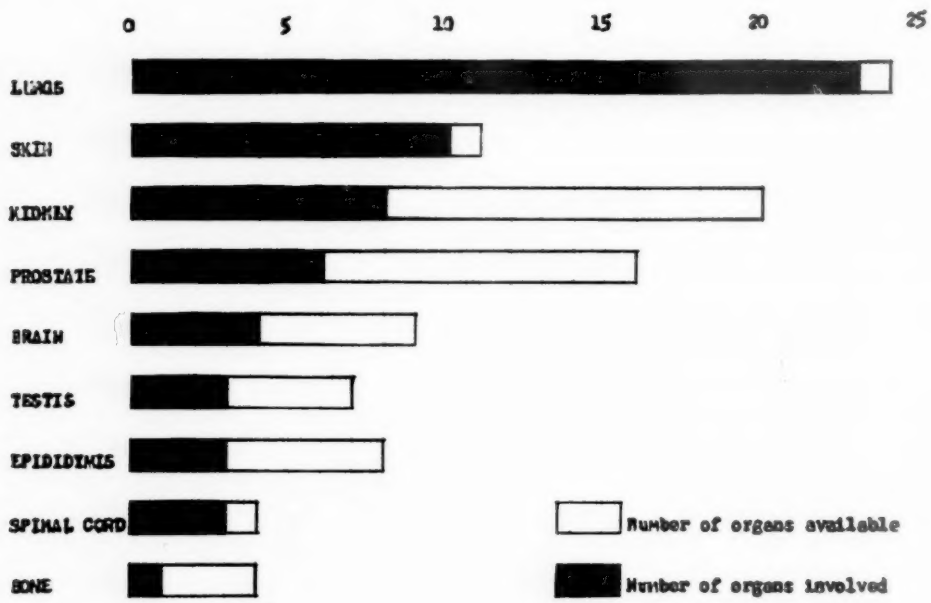

Chart I.—Post-mortem findings in twenty-five cases of blastomycosis.

CASE REPORTS

CASE 1.—J. G., an 89-year-old white man, several days following injury to his right thigh in January, 1950, developed two abscesses in the traumatized area, with subsequent ulceration. On admission to Cincinnati General Hospital in April, 1950, he presented a 2 by 3 inch fungating lesion on the inner surface of his right thigh. Scrapings revealed *B. dermatitidis.* Blastomycin skin test was positive, and chest film showed probable right lower lobe involvement. The lesion of the thigh was excised and a skin graft applied. Up to January, 1952, there had been no recurrence. Sputum examination in March, 1951, was negative.

CASE 2.—G. R., a 67-year-old Negro man, was admitted to Cincinnati General Hospital in July, 1950, with a four-month history of a granulating, encrusted area on the left cheek. Cauterization was performed about two months prior to admission with rapid recurrence. Scrapings and biopsy of the excised lesion revealed *B. dermatitidis.* The area was skin-grafted and the patient given heavy doses of iodides for about one month. Skin test was positive, and chest roentgenogram revealed a probable pulmonary lesion at that time. Up to January, 1952, the grafted area had remained well healed.

CASE 3.—D. W., a 34-year-old white man, noted an enlarging sore at the outer angle of his right eye (Fig. 1) in June, 1950. Five weeks later he experienced sharp lower left chest

pain and a nonproductive cough, which symptoms persisted. Pus taken from the skin lesion in August, 1950, revealed *B. dermatitidis*. Chest roentgenogram demonstrated probable left lower lobe involvement. In October, 1950, the cutaneous lesion was excised and the area skin-grafted. Culture of bronchial aspiration in January, 1951, was positive for Blastomyces. Skin test at this time was also positive. On March 26, a left thoracotomy, performed with the intention of removing a possible isolated pulmonary lesion, revealed an abscess of the chest wall involving two ribs, posteriorly. The involved portions of ribs were excised and the abscess drained. In spite of gross pleural contamination by pus, there was no subsequent demonstrable pleural effusion, and the incision healed per primam. Culture and biopsy, obtained at surgery, were positive for *B. dermatitidis*. In view of the downhill course of the patient, oral ethyl vanillate therapy[4] was begun in April, 1951, and discontinued six weeks later with no apparent alteration in the course of the disease. Up to 28 Gm. a day were given but the maximum blood level obtained was only 5 mg. per cent. Beginning Aug. 22, 1951, 150 mg. of stilbamidine were given intravenously daily for seven days.[26] Toward the end of this course, the patient became toxic and developed jaundice. He died on Sept. 1, 1951. At autopsy diffuse hepatic necrosis was found as cause of death. Blastomycotic lesions were found in the left lower lung, hilar lymph nodes, pons, and thoracic vertebrae and paravertebral soft tissue. The grafted area near the right eye had always remained well healed (Fig. 2).

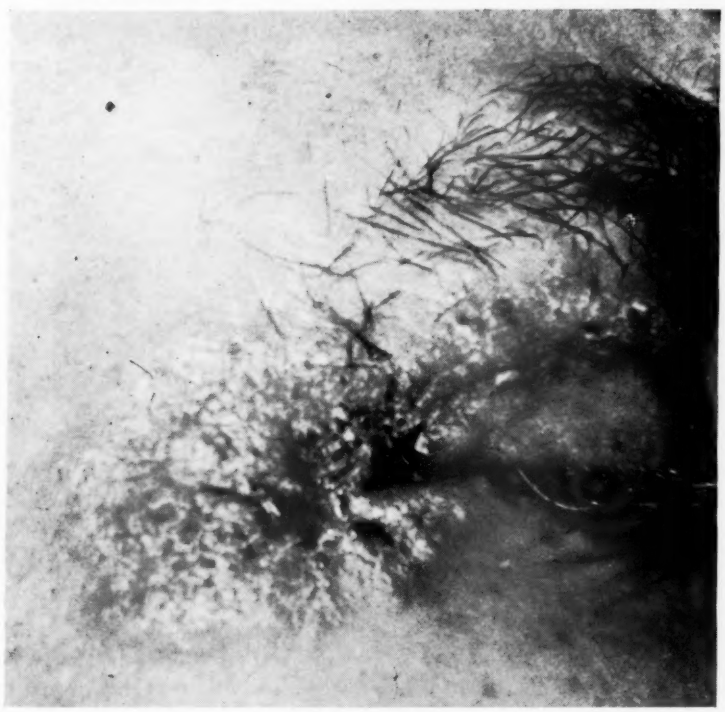

Fig. 1 (Case 3).—Blastomycotic lesion involving upper and lower eyelids.

CASE 4 (previously reported by Smith and Suder[29]).—S. B., a 72-year-old Negro man, in 1933 noted a crusted sore at the base of his left fourth toe. It spread to involve all the toes on the left and also appeared on the right foot. He was seen at Cincinnati General Hospital in 1936. Biopsy of the left foot revealed nonspecific inflammation and this lesion was treated with x-ray. The lesion of the right foot was excised, following microscopic diagnosis of blastomycosis, and pinch grafts were applied. The areas on both feet were completely healed on discharge. In January, 1937, a few weeks following trauma, the patient developed a granulomatous lesion of the left leg. He was seen at Cincinnati General Hos-

pital in May, 1937, at which time biopsy of the lesion showed blastomycosis. Excision of the area plus skin-grafting resulted in healing. There also had been a recurrence of the lesions of the left foot and these were again successfully treated with x-ray. In June, 1949, the patient was seen with a draining lesion of the right side of the scrotum. The right epididymis and prostate gland were hard and nodular. Intravenous pyelograms were negative. In January, 1950, culture of the drainage and prostatic fluid, and biopsy of the fistulous opening were all positive for *B. dermatitidis,* but the lesions of the feet and leg had remained well healed. In April, 1950, a chest film showed right apical infiltration which had also been present in a 1937 film. Subsequently, the patient received intravenous iodides. There was gradual improvement in the scrotal lesion until by November, 1951, there was only scanty intermittent drainage. Up to January, 1952, all grafted and x-ray treated areas had remained well healed.

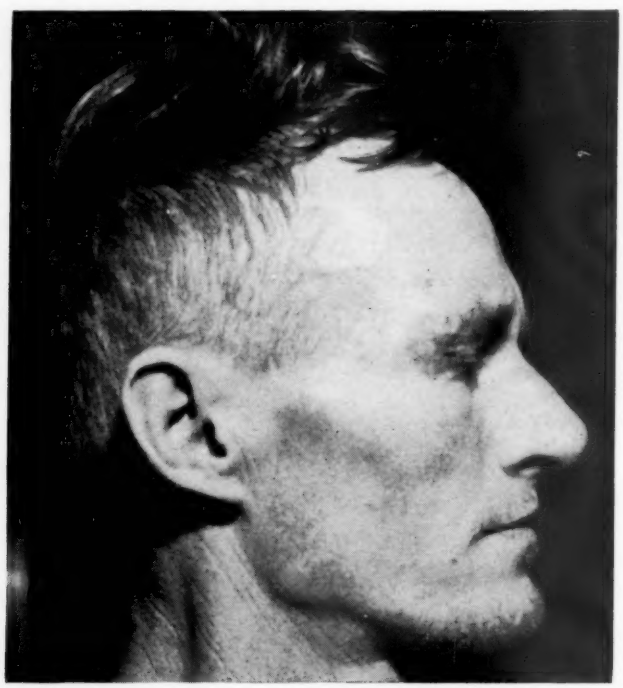

Fig. 2 (Case 3).—Results of excision and skin grafting eight months postoperatively.

CASE 5.—H. S., a 36-year-old white man, was admitted to Good Samaritan Hospital in February, 1950, with a two-year history of recurrent pain and swelling of the right ankle, accompanied by fever. X-ray examination revealed osteomyelitis of the calcaneus. A chest roentgenogram was negative. *B. dermatitidis* was recovered in pus obtained from surgical exploration one week after admission. Biopsy was also positive. A mid-calf amputation was performed in April, 1950. Blastomycin skin test in November, 1950, was positive. Up to December, 1951, the stump had remained well healed.

CASE 6.—H. R., a 53-year-old white man, developed nodules of the left anterior chest wall in April, 1950, which subsequently broke down to form an ulcerating granulomatous area about 3 inches in diameter, biopsy of which revealed blastomycosis. After admission to Cincinnati General Hospital, the patient improved slightly under iodide therapy. The lesion was excised and skin-grafted in December, 1950. It healed slowly, but was satisfactory on discharge in April, 1951. Chest film in January, 1950, revealed infiltrate in the right upper lobe but this had disappeared one year later. Skin test on Nov. 9, 1950, was positive. The skin lesions had remained completely healed by January, 1952 (Fig. 3).

CASE 7.—B. K., a 39-year-old white man, in July, 1948, was admitted to Good Samaritan Hospital with blastomycotic lesions of the upper lip, right forearm, and right groin. Iodides were administered and the lesions of the lip and arm cleared. That of the groin was excised with no recurrence up to May, 1951. No further follow-up is available.

CASE 8.—H. T., a 74-year-old white man, was admitted to Good Samaritan Hospital in December, 1947, with a six-month history of a fungating lesion of the left foot. Biopsy and culture showed *B. dermatitidis.* He was treated with x-ray and streptomycin with temporary regression. Excision and skin-grafting were performed satisfactorily six months later. However, his whereabouts have been unknown since that time.

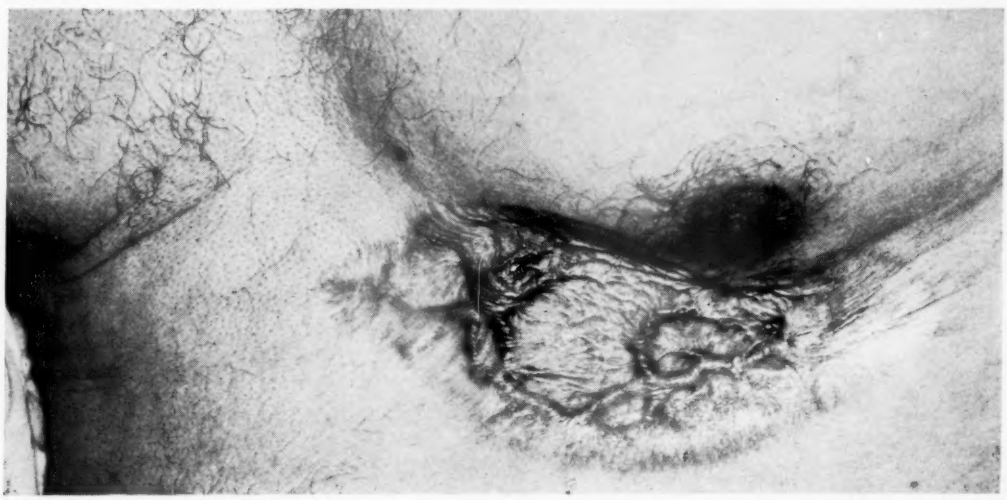

Fig. 3 (Case 6).—Results of excision and skin grafting of blastomycotic lesion of chest wall thirteen months postoperatively.

The next case demonstrates how delaying early surgery in an operable skin lesion results in extensive blastomycotic skin involvement requiring a relatively extensive operative procedure.

CASE 9.—F. M., a 48-year-old white man, entered Cincinnati General Hospital in May, 1951, with an eleven-month history of an enlarging, ulcerated, encrusted patch in front of the right ear, beginning as a "pimple" and steadily growing. On admission, the area measured 6 by 4 inches, extending from the ear to the eye and involving most of the cheek (Fig. 4). Skin test was negative. Microscopic examination of the exudate was positive for *B. dermatitidis.* Chest film was negative. The patient was treated with iodides, with some immediate improvement, but growth of the area then slowly continued. In spite of the size of the lesion, complete surgical excision of the area with grafting was performed in November, 1951, with good results noted two months afterward (Fig. 5).

The following case, though not treated by surgery, demonstrates a surgical condition, acute urinary retention:

CASE 10.—J. B., a 54-year-old Negro man, in March, 1950, developed a productive cough. Two months later, he had lost 37 pounds and demonstrated râles in both lung bases. Chest film revealed a nodularity throughout both lung fields. In September, 1950, the patient developed acute urinary retention. Prostatic secretions yielded *B. dermatitidis.* A retention catheter was inserted. Shortly thereafter, disseminated skin lesions appeared. Subsequently, a soft mass was noted in the right side of the scrotum. In October, he was

admitted to Cincinnati General Hospital for desensitization with blastomycin and treatment with iodides and radioactive iodine. In November, 1950, skin test was positive. The sputum was positive for Blastomyces. The patient died on Nov. 8, 1950, and post-mortem examination revealed blastomycotic pneumonitis, prostatitis, pericarditis, pyelonephritis, meningitis, neuritis, and skin involvement. There was also a suppurative orchitis and epididymitis.

Fig. 4.

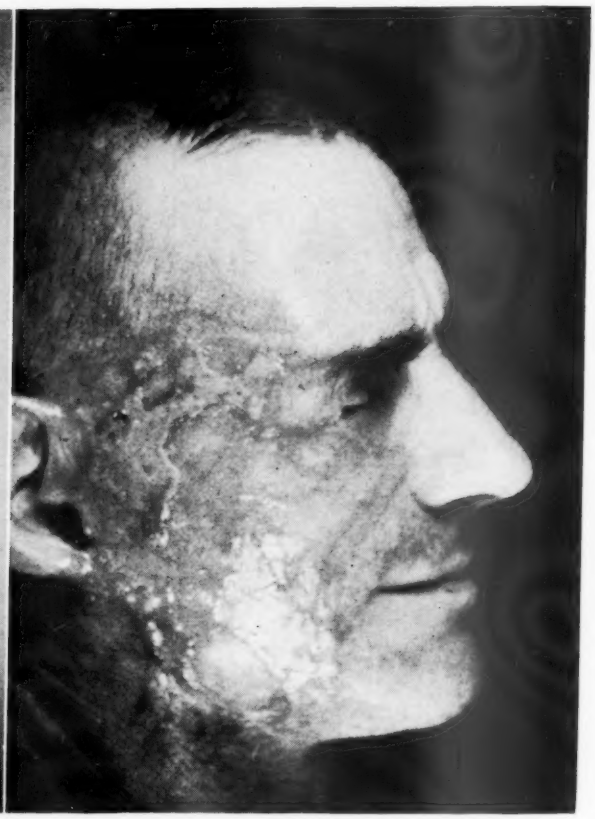

Fig. 5.

Fig. 4 (Case 9).—Blastomycotic lesion of face.
Fig. 5 (Case 9).—Results of excision and skin grafting two months postoperatively.

COMMENTS

Surgery is the therapy of choice in localized blastomycosis. This is borne out both in the literature and in the present series. One must realize that far-advanced disseminated cases are not candidates for surgery and that the value of surgical therapy can be realized only before this situation occurs.

Since blastomycosis is most often primary in the lung, a peripheral focus must be looked on essentially as a metastatic lesion. Therefore excision of such a lesion does not eradicate the disease completely unless it be primary.[9] However, as evidenced by Case 4, arrest of lung lesions may occur. It then follows that if surgical removal of isolated skin or peripheral bone lesions is accomplished, the body may be able to overcome the lung infection and the patient be cured.

TABLE I. RESULTS OF SURGICAL THERAPY IN NINE CASES OF BLASTOMYCOSIS

CASE	EXTENT OF DISEASE	SURGERY	RESULT	FOLLOW-UP
1.	Skin lesion of right thigh Probable right lower lung involvement	Excision of skin lesion and grafting	Good	21 months
2.	Skin lesion, left cheek Probable lung involvement	Excision of skin lesion and grafting	Good	18 months
3.	Skin lesion near right eye	Excision of skin lesion and grafting	Good	11 months
	Lung involvement Left posterior chest wall abscess	Exploratory thoracotomy with partial removal of two ribs and drainage of abscess	Patient died	
4.	Skin lesions both feet, left leg, and right side of scrotum Granuloma, right testicle Probable right upper lung involvement	Excision of skin lesions (of feet and leg) and grafting	Good	15 years
5.	Osteomyelitis, right calcaneus	Mid-calf amputation	Good	20 months
6.	Skin lesion, left anterior chest wall	Excision of skin lesion and grafting	Good	13 months
7.	Skin lesions, upper lip, right forearm, right groin	Excision of skin lesion of groin	Good	3 years
8.	Skin lesions, left foot	Excision of skin lesions and grafting	Good	None
9.	Skin lesion, right side of face	Excision of skin lesion and grafting	Good	2 months

Dissemination of blastomycosis occurs generally from a primary lung lesion.[27] However, any focus of active infection, even if metastatic, can itself act as a center for further dissemination. Removal of such foci is desirable and should be carried out whenever feasible.

The chronic progressive nature of blastomycotic skin lesions and the disfigurement which follows them is well known (Case 9). Even though active disease is present in internal organs, removal of peripheral skin lesions and subsequent grafting frequently results in healing of these cutaneous areas (Case 3). This prevents not only severe cosmetic deformity but also infectious ulceration and is of value even though a cure or an arrest of the disease should not be obtained.

The mode of transmission of blastomycosis is not known. Infection occurs in the respiratory tract, but the source of the Blastomyces is still conjectural. Certainly an ulcerating skin lesion with exudate rich in organisms must be considered dangerous from an epidemiologic standpoint. In light of this, the wisdom of surgically removing the lesion and decreasing the risk of infection of family and medical and nursing personnel is obvious.

Obstruction of the urinary tract is a relatively common surgical problem. Blastomycotic prostatitis with attendant urethral block was encountered in Case 10 and the diagnosis made from prostatic smear. In such cases the surgeon helps make the diagnosis in addition to treating the urinary obstruction.

Medical treatment of blastomycosis has often been disappointing. Iodides and x-ray therapy have helped dry and shrink skin lesions. Antibiotics have been ineffective in treating skin lesions and, along with iodides and x-ray therapy, of no value in widespread disease. Many other agents have been used with essentially the same failure.

SUMMARY

1. A review of the treatment of blastomycosis in the literature and in a series of cases reviewed by us is presented.

2. Surgical removal of peripheral blastomycotic lesions is indicated on the basis of the following:

A. If single or isolated peripheral lesions exist, their removal might result in cure, dependent on the arrest of the primary pulmonary lesion.

B. Active peripheral lesions, though secondary, may themselves act as foci for further dissemination.

C. Blastomycotic skin lesions may cause severe disfigurement.

D. Ulcerating skin lesions may be dangerous epidemiologically.

3. In blastomycotic urinary obstruction the surgeon may be instrumental in making the diagnosis as well as relieving the symptoms.

4. Of all methods of treatment in localized blastomycosis, surgery is of most practical value.

Acknowledgments.—Cases 1, 3, 4, and 9 were made available to us through the courtesy of Dr. L. Goldman and Dr. J. Stevenson; Cases 2 and 6 through the courtesy of Dr. Goldman; Case 3, of Dr. Macht and Dr. E. McGrath; Cases 7 and 8, Dr. W. Germain; Case 5, Dr. Germain and Dr. N. Giannestras; and Case 9, Dr. E. Gall.

All of the cases in this publication are included in the report by Schwarz and Baum.[27] Case 4 was reported previously by Smith and Suder.[29]

REFERENCES

1. Alfred, K. S., and Harbin, M.: Blastomycosis of Bone, J. Bone & Joint Surg. 32: 887, 1950.
2. Babcock, W. W.: Principles and Practice of Surgery, Philadelphia, 1944, Lea & Febiger, p. 140.
3. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, ed. 2, Philadelphia, 1947, J. B. Lippincott Company, p. 514.
4. Christie, A., Middleton, J. G., Peterson, J. C., and McVickar, D. L.: Treatment of Disseminated Histoplasmosis With Ethyl Vanillate, Pediatrics 7: 7, 1951.
5. Cole, W. H., and Elman, R.: Textbook of General Surgery, ed. 5, New York, 1948, D. Appleton-Century Company, Inc., p. 111.
6. Colonna, P. C., and Gucker, T.: Blastomycosis of the Skeletal System, J. Bone & Joint Surg. 26: 322, 1944.
7. Craig, W. M., Dockerty, M. B., and Harrington, S. W.: Intravertebral and Intrathoracic Blastomycoma Simulating Dumb-bell Tumor, South. Surgeon 9: 757, 1940.
8. Dennis, F. L.: Blastomycosis of the Upper Respiratory Tract With Report of a Case Primary in the Larynx, Ann. Otol., Rhin. & Laryng. 27: 571, 1918.
9. Evans, N. A.: Clinical Report of a Case of Blastomycosis of the Skin From Accidental Inoculation, J. A. M. A. 40: 1772, 1903.
10. Gaspar, I.: Blastomycotic Meningo-encephalitis, Arch. Neurol. & Psychiat. 22: 475, 1929.
11. Gaspar, I., Fenstermacher, W. A., and Lingeman, L. R.: Systemic Blastomycosis, With Report of a Fatal Case, Radiology 18: 305, 1932.
12. Hamblen, E. C., Baker, R. D., and Martin, D. S.: Blastomycosis of the Female Reproductive Tract, Am. J. Obst. & Gynec. 30: 345, 1935.
13. Hart, D., in Waters, W.: Lewis' Practice of Surgery, Vol. V, Hagerstown, Md., 1951, W. F. Prior Company, Inc., p. 190.
14. Hass, S. L., in Waters, W.: Lewis' Practice of Surgery, Vol. II, Hagerstown, Md., 1951, W. F. Prior Company, Inc., p. 168.
15. Hemphill, J. E., and Noojin, R. O.: North American Cutaneous Blastomycosis Treated With Superficial Roentgen Therapy, Am. J. Roentgenol. 48: 643, 1942.
16. Homans, J.: Textbook of Surgery, Springfield, Ill., 1948, Charles C Thomas, p. 169.
17. Jackson, C.: Blastomycosis of the Larynx, Arch. Otolaryng. 3: 99, 1926.
18. Jones, R. R., and Martin, D. S.: Blastomycosis of Bone, SURGERY 10: 931, 1941.
19. Ladany, E.: Cutaneous Blastomycosis, North American Type, New York State J. Med. 48: 1281, 1948.

20. Lyle, H. M.: A Case of Blastomycetic Dermatitis, Kansas City M. Index-Lancet 26: 329, 1905.
21. Moore, M., and Halpern, L. K.: Blastomycosis Involving the Prostate: Report of Two Cases, One With and One Without Cutaneous Lesions, J. Urol. 60: 612, 1948.
22. Oliver, E. A., in Christopher, F.: Textbook of Surgery, ed. 5, Philadelphia, 1949, W. B. Saunders Company, p. 82.
23. Ormsby, O. S., and Finnerud, C. W., in Waters, W.: Lewis' Practice of Surgery, Vol. XII, Hagerstown, Md., 1951, W. F. Prior Company, Inc., p. 31.
24. Ormsby, O. S., and Montgomery, H.: Disease of the Skin, ed. 7, Philadelphia, 1948, Lea & Febiger, p. 1169.
25. Rypins, E. L.: Blastomycosis of the Skeletal System, Radiology 22: 77, 1934.
26. Schoenbach, E. B., Miller, J. M., Ginsberg, M., and Long, P. H.: Systemic Blastomycosis Treated With Stilbamidine, J. A. M. A. 146: 1317, 1951.
27. Schwarz, J., and Baum, G. L.: Blastomycosis, Am. J. Clin. Path. 21: 999, 1951.
28. Smith, D. T.: Immunologic Types of Blastomycosis: A Report on Forty Cases, Ann. Int. Med. 31: 463, 1949.
29. Smith, P. G., and Suder, G. L.: Blastomycosis of the Epididymis and Prostate, Urol. & Cutan. Rev. 54: 398, 1950.
30. Stevenson, J. M.: Personal communication.

FLUORESCEIN TEST FOR INTRAPERITONEAL RUPTURE OF THE URINARY BLADDER

Experimental Study

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RUPTURE of the urinary bladder is a surgical emergency. It is imperative to make the diagnosis within a few hours. A high death rate in intraperitoneal rupture of the urinary bladder has been due largely to failure in recognizing the condition sufficiently early, so that an operation could be performed before the spread of infection. The seriousness of disseminated contamination of the peritoneal cavity, and its prevention by early interference, is illustrated by Negley's[9] findings; the mortality in operations performed within the first twelve hours was 11 per cent, whereas in the second twelve hours it had risen to 22 per cent, and by the second day to 43 per cent. Similar tabulations have been reported by Rouvillois and Ferron.[10]

Bacon[1] has shown that the interval between the time of injury and the surgical intervention averaged nineteen and eight-tenths hours. The shortest interval was two hours, and the longest 192 hours. The figures reflect a surgical mortality rate of 36.5 per cent, while the total mortality rate was 44.2 per cent.

One of the tests for diagnosing rupture of the urinary bladder is the injection of a known quantity of fluid into the bladder by means of a catheter for the purpose of detecting if it all returns. This is of some definite value. However, it may lead to an erroneous conclusion, for in some cases where there is an extensive tear it is not uncommon to recover either the entire amount, or a greater quantity of fluid than previously injected. This has been reported by various authors,[2, 3, 7] and can be explained by the findings of Cahill[3] that free fluid in the abdomen is demonstrable in 30 per cent of the cases. Occasionally, a catheter penetrating through an intraperitoneal rupture will drain large amounts of fluid.

Cystoscopic examination has been advocated by some authors to demonstrate rupture of the urinary bladder. Often, definite determination of rupture has been impossible on account of bleeding, or the inability to keep the bladder sufficiently well distended to visualize the perforation. Eisendrath and Rolnick[5] condemn the use of the cystoscope because of the danger of additional shock and infection. This procedure is limited to those trained in the use of this instrument.

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Vaughn and Rudnick[12] have introduced vesicle pneumoradiography as a method of diagnosis. They advocate the injection of 5 c.c. to 100 c.c. of air into the bladder, then the taking of lateral roentgenograms. A concomitant intestinal rupture may be responsible for intraperitoneal air unless one has previously ruled out its presence. Here again the use of special apparatus is required; however, it is not always available.

The injection into the urinary bladder of a radiopaque substance such as 4 per cent sodium iodide[6] or a 5 to 10 per cent hippuran solution, followed by a series of cystograms, has been used with some success in diagnosing bladder rupture. The necessity of x-ray equipment and expert interpretation is the main drawback of this method.

The foregoing criticisms led us to search for a test which would be simple in administration, foolproof in its interpretation, requiring no specially trained personnel or elaborate apparatus. The rapidity of absorption of fluids from the peritoneal cavity has been shown by experiments of Dandy and Rowntree[4] and by Narat and co-workers[8] to be almost instantaneous. These facts suggested to us the employment of a dye which is nontoxic, rapidly absorbed from the peritoneal cavity, and easily detected grossly from a sample of blood. Fluorescein met the above requirements. It was thought that, in the presence of an intraperitoneal rupture of the urinary bladder, a fluorescein solution instilled through a urethral catheter would pass through the rupture into the peritoneal cavity and be absorbed by the peritoneum. The dye could then be detected in a blood sample. To evaluate this procedure the following experiments were performed.

EXPERIMENTS

Four groups of dogs were used in these experiments. There were ten dogs in the first three groups and three in the fourth group.

In the first group the problem was to prove whether or not fluorescein is absorbed through an intact urinary bladder. The animals were anesthetized with a 3 per cent solution of pentobarbital sodium injected intravenously, using 0.5 c.c. per kilogram of body weight. Thirty cubic centimeters of a 0.5 per cent solution of fluorescein* were instilled into an intact bladder through a urethral catheter. One control blood specimen, and three five-minute interval 10 c.c. blood specimens were obtained by venipuncture from the femoral vein.

In the second group the problem was to determine whether or not fluorescein is readily absorbed from the peritoneal cavity. A metal sound placed in the urethra was pushed through the fundus of the bladder, thus rupturing it. Through a urethral catheter, 30 c.c. of a 0.5 per cent solution of fluorescein were instilled into the urinary bladder. This solution passed freely into the peritoneal cavity through the rent. As in the first group, similar blood specimens were obtained. At the conclusion of the experiment the abdomen was opened to be certain that the bladder wall was perforated.

*Fluorescein was supplied by C. F. Kirk Company, New York, N. Y.

The third problem was to determine whether or not fluorescein is absorbed from a perivesicular space. A midline incision over the space of Retzius was made. The bladder was incised extraperitoneally and the skin was sutured with a continuous water-tight silk suture. Again 30 c.c. of the 0.5 per cent solution of fluorescein were instilled through a urethral catheter into the urinary bladder. This solution readily passed into the space of Retzius. As in the previous experiments, similar blood specimens were obtained.

Omentum may plug the rent in a perforated urinary bladder. The perforation may not be detected by other tests. Our fourth problem was to prove that the omental plug could absorb fluorescein instilled into the urinary bladder. The urinary bladder was delivered through a lower midline incision. A urethral catheter was passed into the urinary bladder. A small incision was made through the fundus of the bladder. The opening was plugged by a piece of omentum which was sutured in place to prevent any leakage from the urinary bladder. As in the previous experiments, 30 c.c. of a 0.5 per cent solution of fluorescein were instilled into the bladder through the urethral catheter. As an added precaution, the fundus of the urinary bladder was kept outside of the peritoneal cavity in order to observe any spillage beside the plug into the peritoneal cavity. Fortunately there was none. Blood specimens were obtained as in the previous three groups.

All blood specimens were centrifuged. The serum was observed both grossly and under a Wood's lamp for the presence of fluorescein.

Human experiments using two groups of ten patients were performed. Here again the authors wished to prove that fluorescein is not absorbed through an intact bladder, but that it is readily absorbed from the peritoneal cavity. A 10 c.c. control blood specimen was obtained by venipuncture from the cephalic or basilic vein. Through a urethral catheter 100 c.c. of a 0.5 per cent solution of fluorescein were instilled into the urinary bladder. Ten cubic centimeters of peripheral blood specimens were obtained at three five-minute intervals.

Following various abdominal surgical procedures, from 10 c.c. to 100 c.c. of a 0.5 per cent solution of fluorescein were instilled into the peritoneal cavity. As in the previous experiments, blood samples were obtained.

All blood specimens were centrifuged. The serum was examined both grossly and under a Wood's lamp. The control specimen was compared with the five-minute interval specimens.

RESULTS

In the first group of animal experiments, no fluorescein was detected in the centrifuged blood specimen either grossly or under a Wood's lamp. This proved that fluorescein in the concentration used is not absorbed through an intact bladder into the blood stream.

In the second group of animals with a perforated bladder, all specimens of blood except the controls contained fluorescein in the serum, thus proving

that fluorescein is readily absorbed from the peritoneal cavity into the blood stream.

In the third group fluorescein was made to pass into the space of Retzius through a rent in the bladder. No fluorescein was detected in any of the blood samples. This reveals that fluorescein in the concentration used is not absorbed from a perivesicular space within the time limit used in the experiment.

In the fourth group in which the omental plug was placed in the bladder, fluorescein was present in all blood specimens except the controls. As would be expected, the concentration of fluorescein was diminished. This finding may be utilized in the differentiation of a ruptured bladder sealed with omentum from one which is not.

Most of the blood specimens containing fluorescein revealed the presence of the dye before centrifuging.

DISCUSSION

In every case of suspected rupture of the urinary bladder, the authors advocate instillation of 100 c.c. of a 0.5 per cent solution of fluorescein through a urethral catheter into the urinary bladder. A previous 10 c.c. control peripheral blood specimen should be taken. It is important to compare the control with the following five-minute specimens, as normal blood serum may have a greenish tint. No error can be made on this account, however, since the serum containing fluorescein is always darker and will fluoresce more. Before centrifuging, it is advisable to defibrinate the blood after it clots.

The clinical picture should be the first clue in the diagnosis of rupture of the urinary bladder. This picture is admirably portrayed by Taylor[11]:

> The onset of symptoms is usually sudden, and the anxious looking patient may inform you that he felt something give inside his abdomen. Shock is usually present at a very early stage, the pulse is weak and rapid, and the systolic blood pressure is in the region of 100 m.m. of mercury. The abdominal pain is sudden and severe, often spasmodic in nature, and is associated with straining and inability to pass urine. The patient suffers from marked urgency, and if he does succeed in passing a small quantity of urine, there is severe dysuria, and possibly marked hematuria. This is later followed by complete retention of urine. Nausea is present and vomiting is usually early and repeated. Hiccup may be present, but does not usually occur until the later stages.
>
> On examination of the abdomen there is rather diffuse abdominal tenderness, and pain is most marked over the hypogastrium. There may be marked rigidity of the abdominal muscles, and recoil tenderness is usually present from the beginning.
>
> In the early stages the presence of urine in the peritoneal cavity is not easy to elicit and dullness when present is not well defined. In the later stages a fluid thrill may be found together with shifting dullness. On rectal examination there is a fullness and marked tenderness in the pouch of Douglass. There is leukocytosis with a relative increase in the polymorphonuclear leukocytes.
>
> If the bladder is very septic at the time of rupture, a generalized fulminating peritonitis develops, the abdomen has a board-like rigidity, and there is no audible peristalsis.

We are working on the same principle as a test for tubal patency in sterility problems.

SUMMARY

1. Experiments on dogs showed that 0.5 per cent of fluorescein is not absorbed from an intact urinary bladder or from a perivesicular space, but is readily absorbed from the peritoneal cavity.

2. Experiments on dogs showed that an omental plug absorbs fluorescein in a decreased amount as compared to that absorbed from the peritoneal cavity.

3. Experiments on human beings showed also that there is no absorption from an intact urinary bladder, but that there is rapid absorption from the peritoneal cavity.

4. Fluorescein instilled in a ruptured urinary bladder is an accurate, simple test for perforation.

REFERENCES

1. Bacon, S. K.: Rupture of the Urinary Bladder, J. Urol. **49**: 432, 1943.
2. Bernard, E. Cohler, and Seidman, Edwin A.: Recurrent Traumatic Intraperitoneal Rupture of Bladder, J. Urol. **62**: 463, 1949.
3. Cahill, George F.: Rupture of Bladder and Urethra, Am. J. Surg. **36**: 653, 1937.
4. Dandy, W. E., and Rowntree, L. G.: Peritoneal and Pleural Absorption With Reference to Postural Treatment, Ann. Surg. **59**: 587, 1914.
5. Eisendrath, D. N., and Rolnick, H. D.: Textbook of Urology, Philadelphia, 1930, J. B. Lippincott Company.
6. Martin, H. W.: Ruptured Bladder—Method of Diagnosis, California & West. Med. **36**: 230, 1932.
7. Mathe, Charles Pierre: Traumatic Rupture of the Bladder, California & West. Med. **42**: 384, 1935.
8. Narat, J. K., Cipolla, A. F., Cangelosi, J. P., and Vincenti, A. L.: Intraperitoneal Drip for Postoperative Administration of Fluids, Arch. Surg. **60**: 102, 1950.
9. Negley, J. C.: Rupture of the Bladder, J. Urol. **18**: 207, 1927.
10. Rouvillois and Ferron: Encyclopédie Française d'Urologie **4**: 89, 1921.
11. Taylor, R. A. Russell: Spontaneous Rupture of the Urinary Bladder, Brit. J. Urol. **20**: 117, 1948.
12. Vaughn, R. T., and Rudnick, D. F.: A New Early Sign of Ruptured Bladder, J. A. M. A. **83**: 9, 1924.

A SATISFACTORY OPERATING TABLE FOR USE IN EXPERIMENTAL SURGERY

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THE purpose of this article is to describe the type of operating table used in the Experimental Surgical Laboratories of the University of Washington School of Medicine. Several surgeons have expressed interest in this unit. It has been suggested to us that a brief description of its features should be published.

The unit was designed by one of us (K. A. M.) with Mr. Howard Moore of the Sheet Metal Shop of the University. This project was initiated because of a general dissatisfaction with operating tables used in experimental work. Most units are ordinary four-legged tables with level or V-shaped tops and are stationary. When large animals are utilized, an accessory back table must be available. Furthermore, only conventional positioning of the animal on the table is possible. Unorthodox operative procedures sometimes necessitate positions not easily obtained with the conventional table. Therefore, a table combining all features which are considered desirable was designed. The following is a description of this unit.†

GENERAL DESCRIPTION

The over-all length (including drop-leaf attachment) is 82 inches. The average height is 36 inches. The table weighs 290 pounds. The table consists of a swivel and lift, and 3 separate tables or stands; the main operating table, the drop-leaf work or back table, and an instrument table (see Fig. 1). These will be described in more detail.

The entire table, except for the dental chair hydraulic pump and swivel joint, is made of No. 18 gauge stainless steel sheeting. Rigid, light, yet sturdy construction is obtained by reinforcements made of the same material turned into angles or other geometric designs. All permanent joints are either electrically welded or soldered.

The type of material used in constructing the table is recommended not only because it is relatively light and durable, but also because it can be hosed with water and scrubbed without fear of rust damage.

SWIVEL AND LIFT

The adjustment device is composed of two units: a dental chair hydraulic pump and a swivel which can be locked in any position of adjustment. The swivel is mounted on the end of the dental chair pump shaft, and the entire

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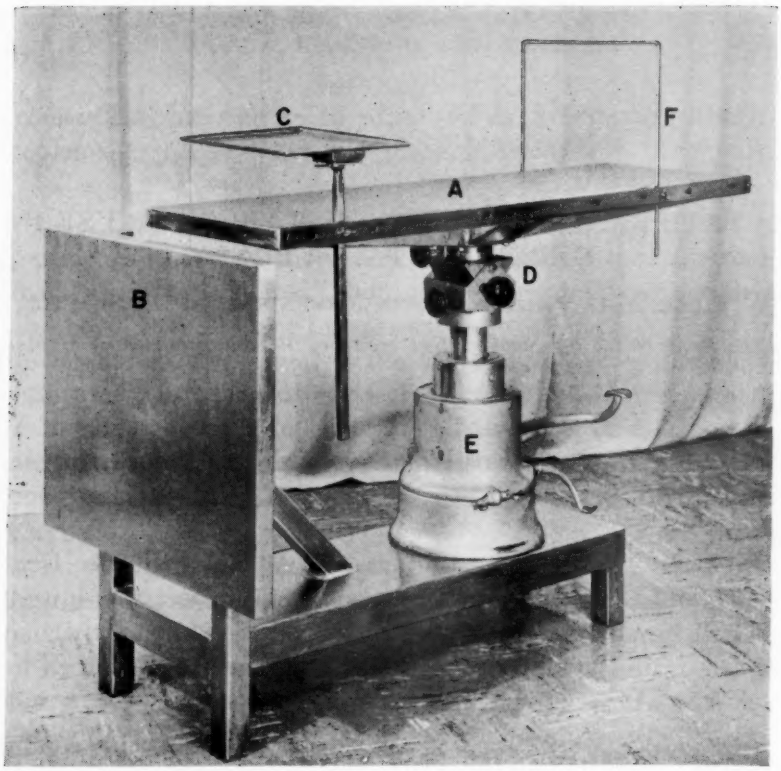

Fig. 1.—Operating table. *A*, Main table, *B*, drop-leaf table, *C*, Mayo stand, *D*, swivel, *E*, dental chair hydraulic pump, *F*, anesthesia screen.

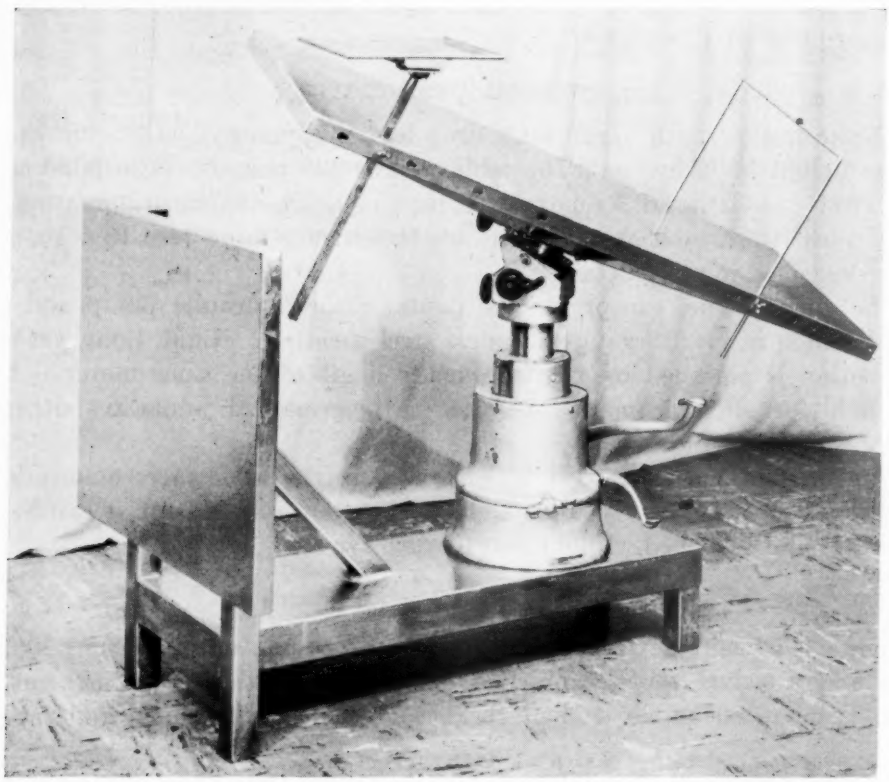

Fig. 2.—Operating table demonstrating versatility. Main table in moderate Trendelenburg position with some, but not maximum, lateral tilt. The table has not been lowered to bottommost position. Mayo stand adjusted to horizontal level. Drop-leaf table positioned for nonuse.

mechanism is bolted to a 46 inch by 14½ inch stainless steel base. The base is raised from the floor on 7 inch legs. Consequently, there is adequate toe space and the area under the table can be cleaned easily.

The dental chair hydraulic pump permits the table top to be raised or lowered a distance of 16½ inches.

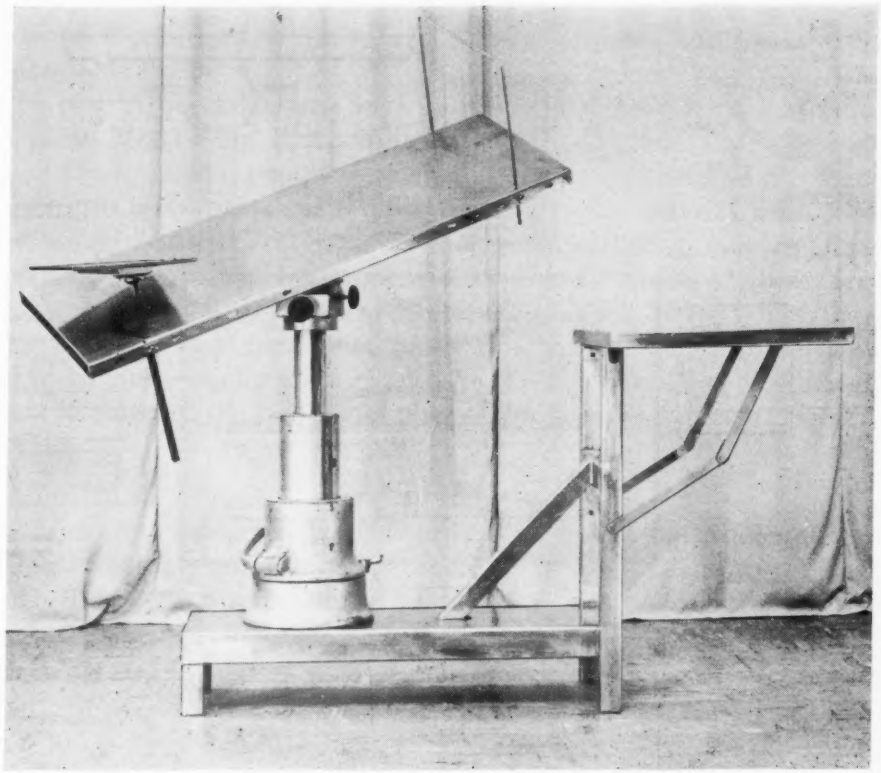

Fig. 3.—Operating table demonstrating versatility. Main table rotated 190 degrees with head-up position with maximum 45 degree tilt. Mayo stand adjusted to horizontal level. Drop-leaf table elevated. The main operating table has been raised to its maximum height from floor.

The swivel, as the name implies, permits universal adjustment. The position may be secured by a leather-lined pressure shoe and a cinch bolt. By the simple adjustment of the knobs on the swivel one may obtain horizontal rotation, elevation of either head or foot to 45 degrees, and rotation of the main operating table in any of the degrees of elevation. Therefore, it is possible to lock the center knob at 45 degrees and, by unlocking the lower knob, rotate the table 360 degrees in the horizontal plane, or, by unlocking the upper knob, rotate the table 360 degrees at a 45 degree angle (see Figs. 2 and 3).

TABLE STANDS

A. The main operating table is 18 inches by 55 inches overall with a 1½ inch turned edge. Multiple keyholes have been made along this edge for securing the rope attachments to the animal. The frame of the table is con-

structed from stainless steel, No. 18 gauge, angulated to give the necessary strength and rigidity. To the central portion of the framework is bolted a swivel adjustment mechanism.

A pair of holes has been made through the top of the main table, 6 and 12 inches from the head, for the anesthetic screen. By means of lateral screws, the height of this screen can be raised or lowered.

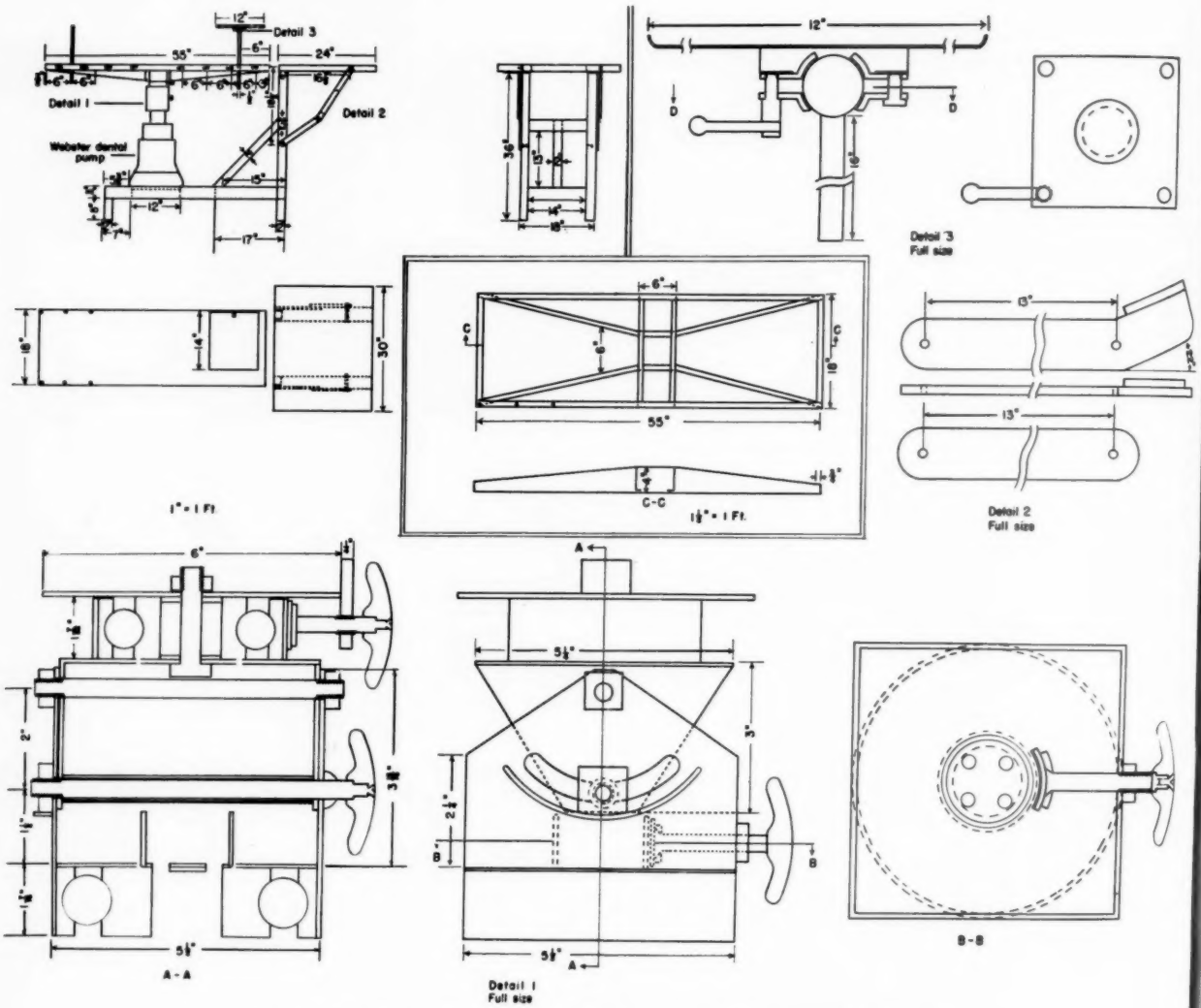

Fig. 4.—Engineering details of the individual mechanical features.

B. Another attachment of the main table is the instrument table (or Mayo stand). It is located on the right-hand edge, 6 inches from the foot. This stand is seen in all views of the main table top and its versatility is well demonstrated. The adjustability of this unit is obtained by a ball-bearing joint with a cinch collar.

C. The drop-leaf worktable (24 inches by 30 inches) is permanently attached to the common base and is supported by 2 rectangular stainless steel

columns with a T-shaped angling brace. It has the advantage of being wider than the main operating table itself. The drop leaf is separated from the main table top by approximately one inch. Consequently, the main table, even when level with the elevated drop table, can be rotated completely without contacting the latter. It is common practice to drape this table as a unit and then set out the boiled tray of instruments. By this method sterile towel clips and other apparatus are available for further preparing the sterile field. The table leaf can be dropped when not in use, thereby allowing additional work space about the table itself.

The cost of the table has been estimated at $250. It was manufactured by the Sheet Metal Shop of the University of Washington. All of the stainless steel and the hydraulic pumps were obtained from war surplus. The universal joints were bought from local scrap dealers. If new material were purchased, the cost would be considerably more. At the present time, four such operating units are utilized in the Department of Surgery. Three of these have been utilized by the Division of General Surgery. On these three tables, over 2,000 major operations have been performed on large animals. These units have proved to be mechanically strong and have given continued good service.

A blue print of the individual mechanical features has been included (see Fig. 4).

SUMMARY

An operating table has been described for use in experimental work. It is durable, compact, and versatile. Some of the valuable features have been stressed. This operating table has been most satisfactory and is recommended for surgical and experimental procedures of all types.

Case Reports

GASTROSCHISIS

Report of Two Cases Treated by a Modification of the Gross Operation for Omphalocele

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An understandable confusion exists in the literature concerning congenital eviscerations through anterior abdominal wall defects due to the lack of a clear and established classification of these anomalies. Furthermore, the large number of descriptive names applied to these malformations has served to hinder the accumulation of a coherent and organized body of reported experience with them. This is especially true with respect to gastroschisis. It is virtually impossible to obtain an accurate picture of the published experience with this specific abnormality through a review of the literature. Many of the reported cases are of fetal and stillborn monstrosities[4, 9, 11, 13] which are both difficult to classify precisely and are of relatively little clinical importance. Others, often notable therapeutic successes, would appear to be more properly regarded as cases of omphalocele.[4, 12] In addition, a number of cases are not sufficiently well described with regard to their distinguishing and differentiating characteristics to permit classification. Some true cases of gastroschisis have, no doubt, been lost in the vast sea of medical publication due to vague titling of the articles. This relatively disordered state of the literature pertaining to gastroschisis has prompted us to formulate a clinical classification of congenital eviscerations through abdominal wall defects which we hope will prove to be of some practical assistance in the future grouping of these cases (Table I).

The principal features of gastroschisis are the extraumbilical location of the defect and the absence of a membranous sac covering the eviscerated mass of intestines. The umbilical cord insertion into the abdominal wall is normal and the umbilical cord is not involved in the evisceration. The appearance of the eviscerated mass has been well described by Berstein.[1] He states that "the absence of a sac results in marked enlargement and thickening of the intestines, with cyanosis, injections and adhesions, firmly matting together clusters of bowel loops; in fact, the entire ectopia presents usually as a large solid mass, consisting of densely adherent abdominal viscera with leathery consistency." In addition, the intestinal loops are often embedded in a rather dense gelatinous matrix.

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TABLE I. CLASSIFICATION OF CONGENITAL EVISCERATIONS THROUGH ANTERIOR ABDOMINAL WALL DEFECTS

1. Omphalocele[8]	(umbilical cord anomaly): Most common. Herniation of viscera into base of umbilical cord. Covering membranous sac or its ruptured remnants present. Umbilical cord insertion into sac. Present at birth.
2. Intussusception of ileum through persistent omphalomesenteric duct[10]	(omphalomesenteric duct anomaly): Rare. Prolapse of inverted mucosa-covered small intestine at umbilicus. Mass often T-shaped. No covering sac. May be present at birth but most often occurs between one and four weeks of age. Often preceded for several days by umbilical fecal fistula.
3. Gastroschisis	(extraumbilical abdominal wall anomaly): Rare. Large eviscerated mass of discolored intestines of leathery consistency. Intestines often embedded in a gelatinous matrix. Normal umbilical cord insertion, the defect being extraumbilical. No covering sac or its ruptured remnants. Present at birth.

The peritoneal cavity is generally quite small in these cases and malrotation of the intestines is frequently encountered. Embryologically, it is known that the anterior abdominal wall is formed by the ventral extension of the lower thoracic and first lumbar myotomes. It is possible that the defect in gastroschisis may result from either a distortion or arrest of this ventral extension.

We have encountered only five reports in the literature which we feel clearly describe cases of gastroschisis in living newborn infants.[1, 2, 5, 6, 14] Others undoubtedly exist. Surgery was attempted in only three cases, and in only one, that recorded by Watkins[14] in 1943, was a successful result achieved.

The unhappy dilemma faced in the operative management of gastroschisis derives principally from the great disparity between the size of the large extracorporeal mass and the considerably reduced capacity of the peritoneal cavity to accommodate it. The problem presented here is quite similar to that encountered in cases of large omphalocele. The impressive results obtained by Gross[3] through the creation of a large ventral hernia by covering the omphalocele sac and its contained viscera with widely undermined skin flaps suggested the applicability of this principle to the treatment of gastroschisis. Secondary repair could then be deferred until sufficient enlargement in the capacity of the peritoneal cavity had occurred with the passage of time. Accordingly, it is felt desirable, due to the rarity of this anomaly and the gravity of the problem faced, to report two cases of gastroschisis in which the utilization of the Gross principle made possible the covering of the large eviscerated masses.

CASE REPORTS

CASE 1.—The patient, a 2-hour-old white female infant, was admitted to the hospital on May 25, 1951, because of a congenital evisceration due to a defect in the anterior abdominal wall (gastroschisis) discovered at birth. There was no family history of congenital abnormalities. The infant was the first child of a 17-year-old mother and a 19-year-old father. She had been born five weeks prematurely and weighed 4 pounds and 1 ounce. Labor had lasted twenty hours. The pregnancy otherwise had been normal.

The patient was mildly cyanotic on admission. A large mass, composed of loops of darkly discolored intestine of leathery consistency embedded in a sizable amount of gelatinous material, was found to be protruding from an oval four-centimeter-long defect in the anterior abdominal wall (Fig. 1). The defect was located approximately two centimeters to the right

of the normal-appearing umbilical cord stump, which was not involved in the evisceration. There was no membranous sac covering the mass and the margins of the defect were rounded and smooth. Multiple areas of apparent small intestinal atresia were encountered on examination of the mass. However, the precise location and extent of atresia could not be determined due to the dense matrix in which the intestinal loops were embedded. No other congenital malformations were identified.

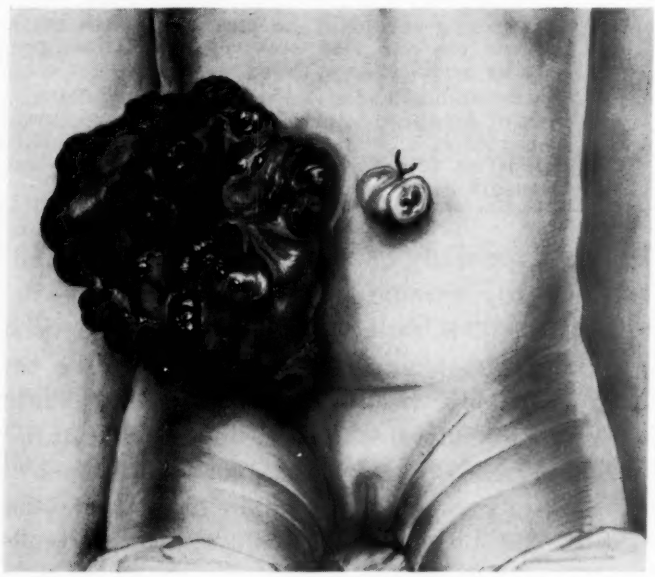

Fig. 1.—Drawing of extracorporeal mass of intestines with multiple areas of atresia (Case 1).

The infant was taken immediately to the operating room. Due to her cyanotic and depressed state, only a small amount of brandy and nasally administered oxygen was given. Limited dissection of the mass readily revealed the inadvisability of this approach. The atresia was so extensive and the loops of intestine so embedded in the firm, gelatinous matrix that injury to both the intestine and its blood supply would be difficult to avoid. For this reason, it was felt that the primary objective should be to cover the mass, deferring definitive attack on the atresia until a later date. Accordingly, the abdominal wall defect was enlarged superiorly and inferiorly and the umbilical cord stump and the tissue between it and the defect were excised. The peritoneal cavity was markedly diminished in size, presumably due to the extracorporeal growth of the bulk of the intestines, and it was immediately apparent that the mass would not be accommodated by the peritoneal cavity as it existed. The most satisfactory means of enlarging the peritoneal cavity to incorporate the mass appeared to be through the use of widely undermined skin flaps and the creation of a large ventral hernia. The skin flaps were dissected around to the back on both sides and were undermined well over the anterior chest wall superiorly and over the pubis inferiorly. The stomach and proximal few centimeters of small intestine were considerably distended with swallowed amniotic fluid up to the point where the intestine became a part of the eviscerated mass. They were emptied by means of suction applied through a Levin tube inserted into the stomach by the anesthetist. There was an absence of normal colonic rotation, leaving the duodenum uncrossed by mesentery or transverse colon. The large intestine was also incorporated in the mass and could not be clearly identified. The skin flaps were brought together over the mass, completely covering it, and were approximatel in the midline with interrupted silk sutures through the skin and subcutaneous tissue (Fig. 2). Tension on the suture line was minimal. The operation was tolerated satisfactorily by the infant.

Continuous gastric suction was employed postoperatively and the patient was maintained by parenteral administration of fluids, electrolytes, dextrose, and whole blood. Penicillin was also given. She did remarkably well with the exception of occasional transitory temperature elevations. The skin flaps fortunately remained viable and their undersurface became endothelialized, as subsequent exploration demonstrated. There was no drainage through the suture line and the wound appeared to be healing well. The sutures were left in place longer than usual because of the nature of the wound closure. Visible peristaltic activity under the skin flaps was first noticed on June 12, eighteen days postoperatively. Roentgenographic studies were carried out on June 13. Instillation of lipiodol into the distal portion of the colon showed it to be patent with a portion of it in the "hernia" sac. Several loops of dilated small intestine were also demonstrated.

Fig. 2.—Postoperative photograph showing appearance of skin flap closure over intestinal mass (Case 1).

Re-exploration was deemed advisable and the patient was returned to the operating room on June 14. Under light, open drop ether anesthesia, the incisional wonnd was reopened. The skin flaps had become endothelialized and were easily separated from the contained intestines. The gelatinous matrix in which the intestines had been embedded had disappeared, presumably metabolized during the long period of gastric suction and parenteral maintenance. Furthermore, the formerly discolored and thickened intestine had become normal both in color and consistency. The small intestine was dilated to the point of atresia in the ileum. The atresia was found to extend to approximately the mid-colon. A side-to-side ileocolostomy, by-passing the area of atresia, was carried out in two layers with 00000 "arterial" silk suture. The stoma appeared to be adequate and the skin flaps were reapproximated with interrupted silk sutures.

Gastric suction and parenteral maintenance were continued postoperatively. Both penicillin and streptomycin were given. The patient passed a stool, her first, on June 15, and again on June 16. On June 17, three days following operation, she began to suffer from progressive respiratory distress, and edema of both the face and extremities was noted. Within a short time the infant had died. Approximately 650 c.c. of intravenous fluids had been given during the three postoperative days.

Post-mortem examination of the lungs revealed a diffuse, patchy atelectasis with superimposed pneumonitis. There was no gross evidence of peritonitis and, although a small tear in the suture line was made during post-mortem dissection, the anastomosis appeared to have been intact. The area of atresia and the malrotation of the intestines were as found at operation. No other congenital anomalies were encountered.

CASE 2.—The patient was a 3-hour-old white male infant who was admitted to the hospital on Aug. 10, 1951, with a congenital evisceration through an anterior abdominal wall defect. The defect had been discovered at birth. The mother was 21 years of age and the father 27. Two siblings were living and well and there had been no previous history of congenital abnormalities in the family. The pregnancy had been normal and of nine months' duration. Labor had lasted five hours and the patient weighed 5 pounds and 11 ounces at birth.

On examination, a mass of intestinal loops was found to be protruding from an oval four-centimeter-long defect in the abdominal wall (Fig. 3). The defect was approximately one and one-half centimeters to the right of the normal-appearing umbilical cord stump and its margins were rounded and smooth. There was no evidence of a membranous sac or its remnants. The loops were matted together with a gelatinous substance which was similar to that encountered in Case 1, but smaller in amount. The involved intestines were dark in color and of a leathery consistency. No other anomalies were encountered.

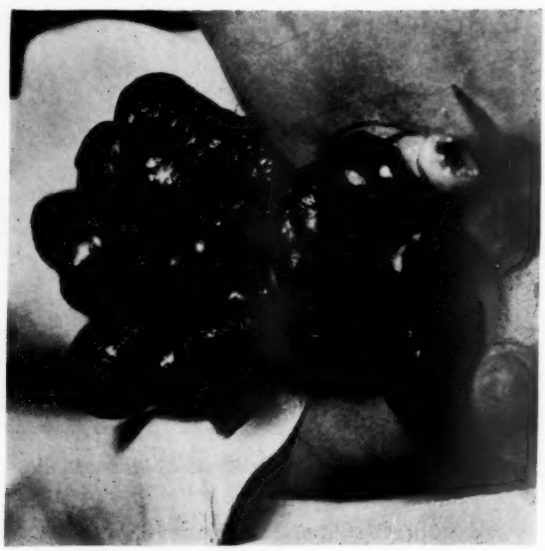

Fig. 3.—Photograph of eviscerated mass of intestines (Case 2).

The patient was taken immediately to the operating room and, under light, open drop ether anesthesia, the defect was enlarged superiorly and inferiorly. The peritoneal cavity was markedly reduced in size and it was quite apparent that it would not accommodate the large, extracorporeal mass of intestines. The umbilical cord stump and the skin between it and the defect were excised. Skin flaps were widely undermined around to the back on both sides and over the chest wall superiorly and the pubis inferiorly. The flaps were approximated with interrupted silk sutures in the midline over the mass of intestines, creating a large ventral hernia similar to that in Case 1. The infant appeared to be in good condition following the completion of this procedure.

Gastric suction and parenteral fluid and electrolyte administration were carried out postoperatively. The infant seemed to be progressing satisfactorily until Aug. 12, two days following operation. At that time he began to show evidence of periorbital edema, cyanosis, and rapidly increasing respiratory difficulty; he died within a few hours. Although the patient had received 650 c.c. of intravenous fluids during the 48 hours following operation, there was no clinical or necropsy evidence of pulmonary edema. The skin flaps had remained in good condition until the time of death.

Post-mortem examination revealed the bulk of the intestines to be within the large, operatively created ventral hernia. The gelatinous matrix was still present and the large

and small intestines were clumped together on a short dorsal mesentery with incomplete rotation. The leathery consistency of the formerly eviscerated intestines remained and, on microscopic study, was found to be due to a thick layer of granulation tissue on the serosa which presumably resulted from the extracorporeal growth of the intestines immersed in amniotic fluid and debris (Fig. 4). There was some patchy atelectasis with mild pulmonary vascular congestion and several alveoli contained epithelial cells of the vernix caseosa. No other anomalies were identified.

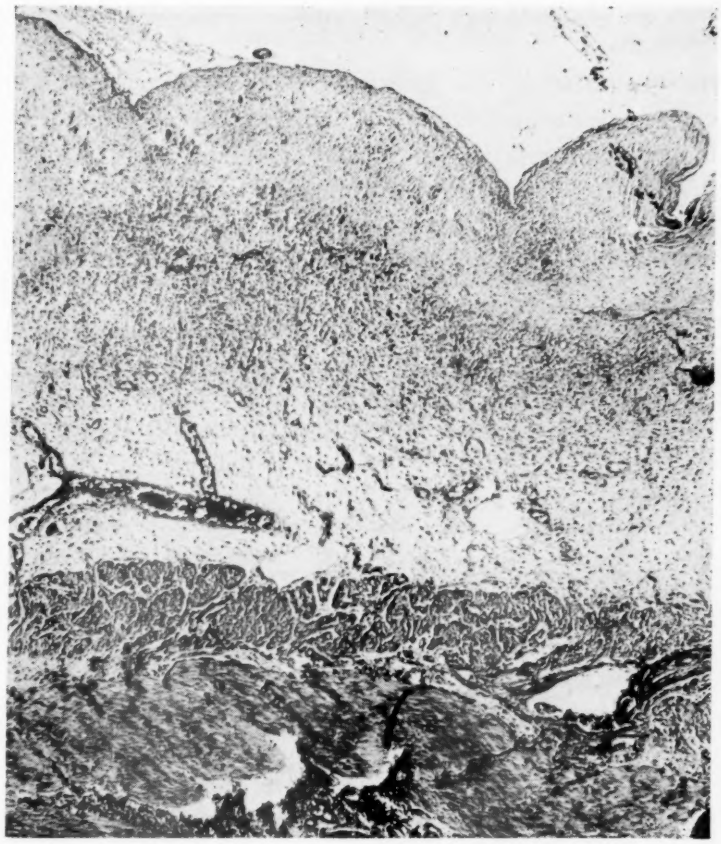

Fig. 4.—Photomicrograph showing thick layer of serosal granulation tissue covering intestine (Case 2).

DISCUSSION

Although both of our patients died, it is quite possible that the first patient might have survived had the case not been complicated further by the presence of extensive ileal and proximal colonic atresias. Nonetheless, it is significant that this patient survived for twenty-three days despite the added handicap. The use of widely undermined skin flaps was obviously the only method by which the large eviscerated masses could be covered and the soundness of this approach is supported by the experience of Gross with large omphaloceles.

Death in both cases presumably resulted from respiratory embarrassment. The occurrence of patchy atelectasis, aspiration pneumonitis, and diaphragmatic compression from below made difficult the maintenance of adequate respiratory exchange. Because of these respiratory hazards and since some degree of dia-

phragmatic compression must be anticipated, upper gastrointestinal tract suction should be carried out to minimize the likelihood of vomitus aspiration, even in cases not complicated by intestinal atresia. Furthermore, the tenuous respiratory status of these patients necessitates considerable caution in the parenteral administration of fluids. Although no post-mortem evidence of pulmonary edema was found in either of our patients, the amount of parenteral fluids given to both patients, particularly the one in Case 2, may have been a contributing factor in their deaths.

Of the cases recorded in the literature, those of Krauss[6] and Calder[2] were considered hopeless and no attempt at surgical repair was made. Both infants died, three hours and four days, respectively, after birth. The patient reported by Koons[5] was born four weeks prematurely. Although his patient was operated upon, the exact nature of the operative procedure was not stated. Death occurred four days following operation and a failure of intestinal rotation was found at necropsy.

Bernstein's[1] patient was born ten days before term and weighed 5 pounds. Bernstein attempted to replace the eviscerated mass by enlarging the defect by an incision through it extending from the xiphoid to the pubis. However, he found that the marked diminution in the capacity of the abdominal cavity prevented even the replacement of the stomach. The patient died shortly thereafter and Bernstein, accordingly, regarded gastroschisis as essentially nonsurgical.

Watkins'[14] successfully treated infant was born two weeks prematurely, weighing 6 pounds. Watkins was able to replace the extracorporeal mass, by enlarging the one inch defect to two inches, and to close the abdominal wall primarily. The patient survived. Watkins attributed his success to the minimal disproportion between the sizes of the mass and the abdominal cavity. A Meckel's diverticulum was also present.

Our first patient and that of Watkins were the only two who survived long enough to permit observations concerning the early functional capacity of the previously eviscerated intestines. Watkins noticed both vomiting and a delay in peristaltic activity in his case. Peristalsis was not found until after prostigmine therapy had been started, six days following operation. Visible peristaltic activity under the skin flaps was not noticed in our case until eighteen days postoperatively. This physiologic inhibition might have been due to the thickening of the bowel wall from the profuse serosal granulation tissue and to the dense gelatinous matrix in which the intestines were embedded. The occurrence of this delay gives added emphasis to the need for gastrointestinal suction until effective peristalsis takes place. Our patient was operated upon shortly after the appearance of peristalsis and radiologic confirmation of distal colonic patency, and it was of interest that the undersurface of the skin flaps had become endothelialized and the leathery consistency of the intestines and the gelatinous matrix had disappeared.

The apparently high incidence of associated malrotation of the intestines is not too surprising in view of the extracorporeal location of the greater portion

of the intestinal tract in gastroschisis. The frequency of this associated anomaly should be borne in mind, especially in cases in which persistent vomiting occurs postoperatively with evidence of duodenal obstruction. In some cases, it may be necessary to carry out the Ladd[7] operation for malrotation of the intestines.

SUMMARY

1. A clinical classification of congenital eviscerations through anterior abdominal wall defects is presented and the differentiating characteristics of the three involved anomalies (omphalocele, intussusception of ileum through persistent omphalomesenteric duct, and gastroschisis) are given.

2. Gastroschisis is described as an extraumbilical abdominal wall defect associated with a large extracorporeal mass of discolored intestines of leathery consistency often embedded in a rather dense gelatinous matrix. The eviscerated intestines are not covered with a sac and the insertion of the umbilical cord into the abdominal wall is normal.

3. The principal difficulty generally encountered in the operative treatment of gastroschisis results from the great disparity in the sizes of the large extracorporeal mass and the abnormally small peritoneal cavity.

4. Two cases of gastroschisis treated by a modification of the Gross operation for large omphaloceles are reported. The extracorporeal mass of intestines was adequately covered by the widely undermined skin flaps in both cases and the flaps remained viable as long as the infants lived. Both patients died, two and twenty-three days postoperatively. The patient surviving twenty-three days had to be operated upon a second time, for extensive associated ileal and proximal colonic atresias. Malrotation of the intestines was found in both cases.

5. Of the five acceptable reported cases of gastroschisis in living newborn infants to be found in the literature, only one was successfully managed surgically, and that by replacement of the intestinal mass into the peritoneal cavity and primary closure of all layers of the abdominal wall. Primary closure was possible in this case because of the minimal disparity in the sizes of the mass and the peritoneal cavity.

6. It is hoped that further experience with the creation of a large ventral hernia by means of covering the eviscerated intestines with widely undermined skin flaps will demonstrate more effectively the merit of this approach to the treatment of cases of gastroschisis of the type heretofore considered inoperable.

7. The hazards to be dealt with in the postoperative management of these patients are discussed.

REFERENCES

1. Bernstein, P.: Gastroschisis, A Rare Teratological Condition in the Newborn, Arch. Pediat. 57: 505, 1940.
2. Calder, J., quoted by Bernstein, P.: Gastroschisis, A Rare Teratological Condition in the Newborn, Arch. Pediat. 57: 505, 1940.
3. Gross, R. E.: A New Method for Surgical Treatment of Large Omphaloceles, SURGERY 24: 277, 1948.
4. Johns, F. S.: Congenital Defect of the Abdominal Wall in the Newborn (Gastroschisis), Ann. Surg. 123: 886, 1946.
5. Koons, F. W.: A Case of Embryonal Ectopia Intestinalis, J. Kansas M. Soc. 35: 136, 1934.

6. Krauss, F.: Zwei seltene Missbildungen, Deutsche med. Wchnschr. **62**: 258, 1936.
7. Ladd, W. E.: Congenital Obstruction of the Small Intestine, J. A. M. A. **101**: 1453, 1933.
8. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, 1941, W. B. Saunders Company.
9. Lippmann, O.: Ein seltener Fall von Spaltbildung der vorderen Leibenswand, nebst Beitrag zur Entstehung von Bauchspalten, Zentralbl. f. Gynäk. **61**: 516, 1937.
10. Moore, T. C., and Shumacker, H. B., Jr.: Intussusception of Ileum Through Persistent Omphalomesenteric Duct, SURGERY **31**: 278, 1952.
11. Pribram, E.: Anteromedian Mero-acrania (Nosencephalos), Combined With Hypogastroschisis Dextra and Malformation of the Fingers and Toes, Arch. Path. & Lab. Med. **3**: 400, 1927.
12. Sauramo, H., and Timonen, S.: Gastroschisis, Acta obst. et gynec. Scandinav. **29**: 79, 1949.
13. Stroer, W. F. H.: Zur Aetiologie der Bauchspalten, Beitr. z. path. Anat. u.z. allg. Path. **106**: 302, 1942.
14. Watkins, D. E.: Gastroschisis, Virginia M. Monthy **70**: 42, 1943.

INTESTINAL ATRESIA IN IDENTICAL TWINS

A Case Report

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THE occurrence of identical intestinal atresias in both of a pair of twins has not been previously reported. Denney and Sloan[3] found congenital intestinal tract anomalies in monovular twins but these deformities were only similar, not identical, in nature. One of the infants had multiple intestinal atresias while the other succumbed to an umbilical hernia and an almost complete atresia of the lower colon.

The rare or previously unreported anomaly may, as a curiosity, merit attention, but the cases here reported deserve consideration for another reason as well. They represent an occurrence which may suggest something of the etiologic nature of congenital intestinal atresia, for the appearance of identical congenital deformities in each of identical twins favors the hypothesis that such a deformity has arisen under the stimulus of genetic, rather than environmental, influences.[4, 11, 19]

CASE REPORTS

Case 1.—J. H. (U. H. No. 826408) was one of identical male twins born to a primipara mother on Dec. 3, 1950, approximately eight weeks prematurely. The infant weighed 1,700 grams. From birth he failed to pass stools and vomited all feedings with bile-stained liquid, hence he was maintained on parenteral fluids and as additional treatment was given vitamin K and penicillin.

The infant's condition failed to improve and, after a tentative diagnosis of bowel atresia was made, he and his twin brother were transferred to University Hospitals when 4 days old.

The infant was jaundiced and thin. The respiratory rate was irregular and there were a few râles auscultated in the right chest. The heart rate was regular and no murmurs were heard. The abdomen was distended and tympanitic and the configuration of bowel loops could be seen through the abdominal wall. Roentgenograms showed a pneumonic infiltration of the right lung and gaseous distention of small bowel loops, suggesting a mechanical bowel obstruction in the lower ileum.

This infant was weaker than his twin, and, though he was a very poor operative risk, he appeared slightly stronger after being given intravenous fluids. Rather than abandon hope of saving him, I operated upon him about sixteen hours after admission.

Under procaine anesthesia locally supplemented with cyclopropane, the abdomen was opened and the distended small bowel was delivered. The cause of obstruction was found to be an occluding membrane at the ileocecal valve, and at a higher level there was an apparently harmless Meckel's diverticulum with a relatively broad base. Air and mineral oil were used to fill the narrow bowel distal to the obstruction by injection with a fine bore needle, but the bowel remained no more than 2 to 3 mm. in diameter. Rather than a side-to-side anastomosis being attempted, the bowel was opened longitudinally over the membrane, the membrane was divided, and repair was completed by closing the bowel wound transversely, after patency of the colon had been determined by noting that methylene blue would pass through it and out the anus.

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After the infant was returned to the incubator his condition was poor, and within a few mintues he began to regurgitate bright red blood. Despite intubation with an intratracheal tube, oxygen, blood, and stimulants, his heart soon stopped beating.

At autopsy there was found pulmonary edema, atelectasis, and pneumonia. There was some fresh blood in the bronchi and in the stomach with some gastric mucosal congestion, but no erosions or ulcers as an obvious source of the hemorrhage. The surgical repair of the intestinal atresia allowed passage of intestinal contents without difficulty.

CASE 2.—G. H. (U. H. No. 826407) was born an identical twin of the infant whose case was described. He weighed 1,750 grams, and at 4 days of age was transferred to University Hospitals with his brother.

His history of vomiting and obstipation was identical to that of his twin and the physical findings were similar, though this child seemed to be slightly more vigorous than his brother. X-ray films showed a pneumonic infiltration on the right and gaseous distention of the small bowel.

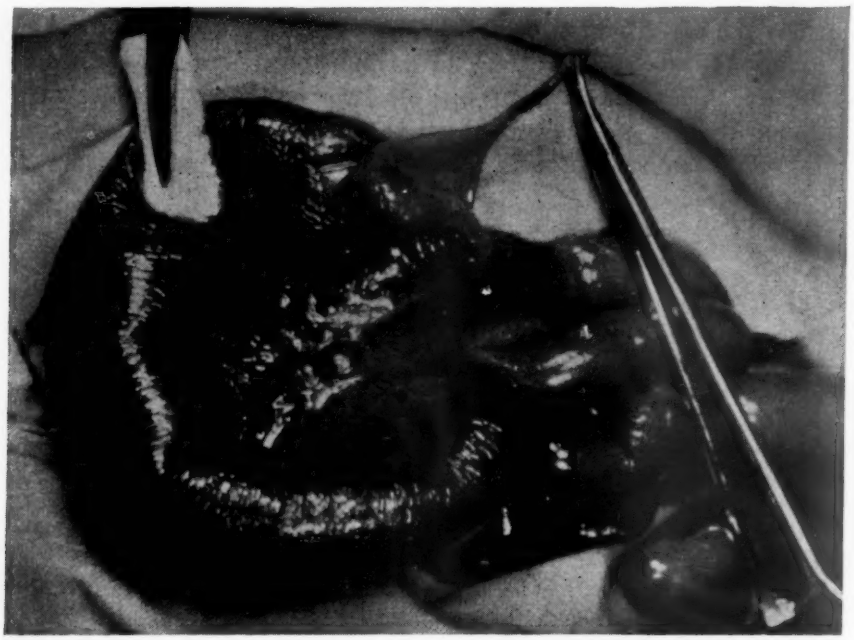

Fig. 1.—View at operation in Case 2. The appearance was identical in Case 1. A hemostat holds the appendix. At the base of the appendix is the tiny cecum with the narrow colon leading away from it to the right. To the left is the greatly dilated ileum with a groove between it and the cecum which indicates the site of the septal atresia.

After eighteen hours of preparation, and following the operation on his brother, the abdomen was opened under local procaine anesthesia supplemented with cyclopropane and an obstruction, identical to that of his brother, was found at the ileocecal junction (Fig. 1). No Meckel's diverticulum was found in this infant. After distending the bowel distal to the obstruction and establishing its patency, the bowel was opened longitudinally, the membrane removed, and the bowel was then closed transversely. Meconium could be milked through the repair and into the narrow colon with ease.

Following surgery his condition remained poor, and, as had occurred before surgery, he continued to have periods of apnea and cyanosis. On the evening of the first postoperative day he began to vomit bright red blood, and this continued until it became increasingly difficult to maintain adequate respiratory exchange. He died on the morning of the second postoperative day.

At autopsy blood was found in the lungs and bronchi and also in the intestine. This blood apparently originated from a small ulcer of the stomach on the greater curvature near the pylorus. The distal ileum was still distended with fluid as it had been at surgery and the absence of liquid in the colon indicated a functional failure of the repair, though at autopsy the ileal fluid could be milked easily into the colon and out through the anus.

DISCUSSION

After the first and weakest twin had been operated upon, I presumed, on the basis of a similar clinical history and the identical nature of the twins, that the second twin would have a similar intestinal defect. In this presumption I was correct; but, despite being armed with the precise diagnosis and with the operative experience so recently gained from an identical problem, I was unable to save even the second twin. Failure in treating this disease is still common and, as it was in these cases, the failure is often attributed to the prematurity of the infants and to the advanced stage which their disease has attained before they finally reach the surgeon.

Though there are still many failures, there has been a gratifying improvement in the treatment of this disease dating back to the work primarily of Ladd,[9, 10] and, as might be expected, recognition of the essential curability of the lesion has drawn increased attention to all aspects of the condition. Particularly intriguing are considerations of the basic etiology of the disease. In fact, concern with the etiology of congenital defects in general has become more common as these diseases have attracted greater attention, this due largely to the decreased seriousness of infectious diseases and the improved surgical methods now used for treating many congenital defects. Yet, with regard to most congenital defects, the basic causal mechanism actually remains obscure.

The most frequently repeated theory explaining the development of congenital intestinal atresia is that an arrest in development takes place during a fetal stage when the intestinal lumen normally becomes obliterated with epithelium and before the lumen is re-established by a process of vacuolization.[10, 18, 21] This theory as an explanation for all intestinal atresias suffers some weakness. Though the process of epithelial occlusion and subsequent vacuolization normally takes place primarily in the duodenum,[8] a large percentage, and in some series the largest percentage, of intestinal atresias occurs in the distal small bowel.[2, 9, 21] Further, though the process of vacuolization does occur normally in the esophagus,[6, 8] septal atresias, such as occur in the lower small bowel, are never found here. As a further difficulty it is hard to understand how a complete disruption of intestinal continuity with a mesenteric defect as well, a type of atresia seen rather commonly, could be due to a persistence of the occlusive stage of intestinal epithelization.

If this theory does not satisfy, there are many others from which one may choose. In fact, a recent article[16] has listed fifteen etiologic theories which have been proposed to explain the cause of congenital intestinal atresia. Despite all these theories, it is notable that in most discussions regarding the etiology of intestinal atresia there is little concern with the question of

whether or not the disease is hereditary in nature. Some of the suggested etiologic agents, such as fetal peritonitis, congenital volvulus, fetal intussusception, and pressure from surrounding organs,[16] by their nature imply a nongenetic basis for the disease. Other proposed etiologic agents, such as the epithelial occlusion theory, for example, may actually be thought of as having beneath them a genetic basis. For these one may consider the etiologic explanation, as it is usually given, to represent a description of only the pathogenic mechanism of what is essentially a genetic causation.

Unfortunately for this theory the evidence at hand apparently does not favor a genetic basis for the disease. There are only a few reports suggesting that intestinal atresia has occurred in more than one member of a family,[1, 5, 17] and these are not well documented. Somewhat stronger evidence in this line is offered by the previously mentioned cases of Denney and Sloan[3] who found intestinal abnormalities in a pair of identical twins, but there still is lacking convincing evidence that the condition follows a clearly hereditary pattern. This may be undetected due to want of good family histories in these cases. In the case reported here, I have been unable to make a satisfactory inquiry into the family medical history. There are also other possible ways of explaining the infrequent family history of the condition even if the disease is primarily hereditary in nature. It has been shown[20] that some hereditary defects carried as dominant traits may express themselves only as minor abnormalities in some generations, or perhaps they may not be evident at all. Further, if the defect is inherited by a recessive mode it may long remain hidden in a family tree.[20] Complicated genetic patterns based on more than one pair of genes would make an hereditary line even more difficult to trace.

It might be assumed that intestinal atresia has an hereditary basis if most other congenital defects were hereditary in nature, but this is not established for there has been considerable difference of opinion concerning the relative importance of heredity or environment in the causation of congenital defects in general. Mall[13, 14] stated unequivocally that pathologic embryos developed from normal ova due to external influences through a condition which he spoke of as faulty implantation. In direct contrast to this idea, more recent opinion, founded on studies of families in which there were congenital defects and on the incidence of defects in pairs of like-sexed and opposite-sexed twins,[12, 15] favors the idea that most human congenital abnormalities arise from factors present in the male or female germ cells prior to fertilization. In fact, Murphy[15] feels that the only nongenetic agents which have been proved to produce human congenital defects are therapeutic amounts of maternal pelvic roentgen or radium irradiation or a maternal attack of rubella during pregnancy. However, the problem still remains complicated and, as Warkany[20] has pointed out, it is quite probable, as suggested by experimental work, that other external, nongenetic influences will in time be shown to produce congenital malformations in human infants.

Present knowledge would make it appear that there are some congenital defects with a definite genetic causation, others caused primarily by environmental factors, and a large remaining group in which the causative factors are

not yet clear.[7] Certainly the unique occurrence of intestinal atresia in twins reported here does little to remove this defect from the vague third group and place it with those in which a genetic causation has been established, but it does suggest the possibility of a genetic basis. Further similar reports and a more thorough study of the family history of the disease would be of considerable interest.

SUMMARY

1. The occurrence of identical septal atresias of the ileocecal junction in each of identical twins is reported.

2. The etiology of this congenital defect, especially with regard to its possible hereditary nature, is discussed.

REFERENCES

1. Cohen, P.: Congenital Intestinal Obstruction With Special Reference to the Value of the Plain Roentgenogram for Diagnosis, Am. J. Dis. Child. **61**: 135-149, 1941.
2. Davis, D. L., and Poynter, C. W. M.: Congenital Occlusions of the Intestines, Surg., Gynec. & Obst. **34**: 35-41, 1922.
3. Denney, E. S., and Sloan, L. H.: Congenital Intestinal Malformations in Identical Twins, S. Clin. North America **12**: 227-240, 1932.
4. Fairweather, D. S., and O'Sullivan, H. J. L.: Gastric Dilatation, Megacolon, and Idiocy in Identical Twins, Arch. Dis. Childhood **22**: 236-241, 1947.
5. Farr, C. E., and Fries, M.: Congenital Occlusion of the Bowel, S. Clin. North America **5**: 621-632, 1925.
6. Forssner, H.: Die angeborenen Darm- und Osophagusatresien. Einen entwicklungsgeschichtliche und patologisch-anatomische Studie, Anat. Hefte. **34**: 1-163, 1907.
7. Fraser, F. C., and Fainstat, T. D.: Causes of Congenital Defects, Am. J. Dis. Child. **82**: 593-603, 1951.
8. Johnson, F. P.: The Development of the Mucous Membrane of the Esophagus, Stomach and Small Intestine in the Human Emryo, Am. J. Anat. **10**: 521, 1910.
9. Ladd, W. E.: The Choice of Time and Type of Operation in Surgery of Early Life, Pennsylvania M. J. **46**: 677-682, 1943.
10. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, 1941, W. B. Saunders Company.
11. Laubscher, J. H., and Smith, A. M.: Pyloric Stenosis in Twins. Review of the Literature and Report of a Case, Am. J. Dis. Child. **73**: 334-341, 1947.
12. Macklin, M. T.: Heredity as the Cause of Congenital Malformations, Am. J. Obst. & Gynec. **32**: 258-265, 1936.
13 Mall, F. P.: A Study of the Causes Underlying the Origin of Human Monsters, J. Morphol. **19**: 1-367, 1908.
14. Mall, F. P.: On the Frequency of Localized Anomalies in Human Embryos and Infants at Birth, Am. J. Anat. **22**: 49-72, 1917.
15. Murphy, D. P.: Congenital Malformations. A Study of Parental Characteristics With Special Reference to the Reproductive Process, Philadelphia, 1947, J. B. Lippincott Company.
16. O'Neil, J. F., Anderson, K., Bradshaw, H. H., Lawson, R. B., and Hightower, F.: Congenital Atresia of the Small Intestine in the Newborn. Report of Two Cases, With a Review of Successfully Treated Intrinsic Obstructions of the Small Bowel, Am. J. Dis. Child. **75**: 214-237, 1948.
17. Rogers, E. J. A.: A Successful Operation for Intestinal Obstruction in an Infant Sixty-four Hours Old, Med. News **71**: 434-437, 1897.
18. Tandler, J.: Zur Entwicklungsgeschichte des menschlichen Duodenum in fruhen Embryonalstadien. Morph. Jahrb. **29**: 187-216, 1902.
19. Wagner, D. H., and Baratz, J.: Pyloric Stenosis in Twins, Am. J. Dis. Child. **81**: 253-255, 1951.
20. Warkany, J.: Etiology of Congenital Malformations, Advances in Pediatrics, Vol. 2, New York, 1947, Interscience Publishers, Inc., pp. 1-63.
21. Webb, C. H., and Wangensteen, O. H.: Congenital Intestinal Atresia, Am. J. Dis. Child. **41**: 262-284, 1931.

INTRAHEPATIC CHOLANGIOJEJUNOSTOMY

Report of a Case With a Two and One-Half Year Follow-up

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(From St. Luke Hospital, Pasadena, Calif.)

THIS case is reported as a successful use of the intrahepatic cholangiojejunostomy[1] in a patient in whom extrahepatic ducts were absent, and on whom standard procedures had been used without effecting a cure. The patient has remained well for two and one-half years following this procedure.

The first two operations were performed elsewhere, and the last two were performed by the authors. Through the kindness of the original surgeon, we have been able to review the hospital records from the first two operations.

CASE REPORT

A 34-year-old woman underwent cholecystectomy on Oct. 6, 1941, at which time the common duct was described as being extremely small and fibrosed, 1 to 2 mm. in diameter. The common duct was opened and explored and a No. 16 French catheter was inserted into the distal portion of the duct with purse-string catgut, and a No. 14 French catheter was inserted into the proximal portion of the duct with purse-string catgut. The operation was extremely difficult and prolonged, and the patient was in profound shock at the end of surgery.

Three days postoperatively there was copious free bile drainage from the biliary wound about the catheters, and this continued until the patient left the hospital. Pathologic examination of the gall bladder was normal. Bile continued to drain for five months with no bile in the stools. Eighteen months after the first operation the patient had her first bout of chills, fever, jaundice, and pain, and these occurred approximately once a month.

In the fall of 1947, the symptoms became more severe and more frequent and the patient was having chills, fever, jaundice, and pain almost constantly. The second operation was performed Sept. 18, 1947. At this time a normal proximal portion of the common duct was found. The lower half of the common duct was not identified. A choledochoduodenostomy was performed and a drain was placed down to the site of anastomosis. There was profuse bloody drainage from the wound for the first four days, at the end of which time the drain was removed. Profuse biliary drainage persisted from the sixth to the eighteenth postoperative day, at which time the patient was discharged. The drainage stopped soon afterward. The patient was symptom free for two months, and then chills, fever, and jaundice returned.

Five months after her second operation, at which time the patient was first seen by us, she was having continuous chills, fever, pain, and jaundice. The third operation was performed March 1, 1948. The usual adhesive mass was encountered, consisting of the liver, stomach, duodenum, transverse colon, and omentum. No biliary ducts were found. The duodenum was opened and a probe was passed through the ampulla of Vater, but the probe stopped in the pancreas. The dissection was carried into the hilus of the liver for 1 inch, and a 7 mm. duct was encountered and was anastomosed to a defunctionalized jejunal limb,[2] 24 inches long, over a Vitallium tube. A drain was placed down to the area of anastomosis. The patient drained bile for fifteen days following this operation, and was asymptomatic for four months, at which time the episodes of chills, fever, pain, and jaundice resumed.

On Oct. 21, 1949, an intrahepatic cholangiojejunostomy was performed. The technique[1] was varied slightly in that the left lobe of the liver was excised with the use of the electrosurgical unit. It was felt that this would lessen the amount of hemorrhage that would be expected from a cold knife excision, and the impression was that this was so. A large duct

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was found, through which a No. 24 catheter was passed for several inches and bile was aspirated. This duct was opened at a point of bifurcation, and the bifurcation was incised and spread, allowing a much larger surface for multiple fine silk sutures. The bile duct was dissected out of the liver for a distance of 1 cm., and an anastomosis was made to the already present defunctionalized arm of jejunum. The anastomosis was made over a Polythene catheter. A cigarette drain was placed down to the area of anastomosis. Before suturing the jejunum to the cut surface of the liver, Gelfoam was placed over the oozing areas in the liver. Postoperatively the patient did extremely well. There was a negligible amount of bloody drainage the first few hours. There was no bile drainage from the wound until Nov. 4, 1949, two weeks postoperatively. There was minimal bile drainage from November 4 to November 29, at which time the wound was dry. The drain was removed on November 9. The pathologic diagnosis of the specimen of the liver sent to the laboratory was biliary cirrhosis. Since November 29 there has been no drainage from the wound. The patient has had no chills, fever, jaundice, or pain and has had no symptoms referable to biliary obstruction.

On Nov. 14, 1951, approximately two years following the last operation, the patient began experiencing abdominal cramping. A Gastrointestinal Series was given at the time and showed no significant abnormalities and no barium going into the defunctionalized loop of jejunum. A few days after this episode the patient became symptom free and passed the Polythene catheter.

Laboratory tests given at St. Luke Hospital, Pasadena, Calif. on April 30, 1952, showed the icteric index was 3, direct bilirubin was 0.15, indirect bilirubin was 0.11, cephalin flocculation was negative at both 24 and 48 hour readings, urinary urobilinogen was positive, prothrombin time was 12 seconds, and control was 12 seconds. When last seen on June 5, 1952, the patient was asymptomatic and a complete physical examination was negative. The red blood count taken at this date was 4,800,000, hemoglobin was 94 per cent, and white blood count was 9,300. The urinalysis was negative.

COMMENT

This patient had gone for eight years with signs and symptoms of recurrent biliary obstruction. She had been hospitalized on eight different occasions. Both choledochoduodenostomy and choledochojejunostomy had been utilized with unsatisfactory results. The patient has been symptom free for two and one-half years following intrahepatic cholangiojejunostomy.[1]

The indications for the operation are admittedly rare, but for the patient with absent extrahepatic ducts it should be considered. Its greatest advantage, we feel, is the accessibility of the duct and jejunum to the surgeon, as it is possible to perform a meticulous anastomosis with mucosa-to-mucosa suture.

SUMMARY

A case of absent extrahepatic ducts with cure by intrahepatic cholangiojejunostomy[1] is reported (thirty-month follow-up). It is suggested by the authors that intrahepatic cholangiojejunostomy is the operation of choice for the admittedly rare case of absent extrahepatic ducts.

REFERENCES

1. Longmire, W. P., Jr., and Sanford, M. C.: Intrahepatic Cholangiojejunostomy, SURGERY 24: 264, 1948.
2. Cole, W. H., Reynolds, J. T., and Ireneus, C.: Strictures of the Common Duct. Ann. Surg. 128: 332, 1948.

LINGUAL THYROIDECTOMY: AN IMPROVED TECHNIQUE

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THE purpose of this paper is to describe an improved technique for the excision of lingual goiter and to present a brief summary of a case in which this technique was used with satisfaction.

CASE REPORT

P. P., a ten-year-old white girl, was admitted to the Medical College of Virginia Hospital on Aug. 15, 1948, complaining of difficulty of speech and interference with swallowing, the result of a mass in the base of the tongue. Four years previously, when the patient's tonsils were removed, this mass was first noted and was thought to be a cyst. Her mother stated that since that time the mass had gradually increased in size, and that during the last six months the child's speech had become thick and her breathing more noisy, especially during sleep. In this same period the patient had noted occasional difficulty in swallowing.

Examination revealed an apparently healthy ten-year-old girl. The only significant physical finding was a firm ovoid mass in the base of the tongue beneath the foramen cecum. This mass almost filled the oropharynx when the tongue was drawn forward. The overlying mucous membrane was quite vascular but otherwise did not appear abnormal. Aspiration biopsy was attempted, but neither fluid nor recognizable tissue cells were obtained. No thyroid tissue was palpable in the neck.

After the administration of radioactive iodine no radioactivity was demonstrable in the area normally occupied by the thyroid gland, whereas considerable radioactivity was found over the lingual mass. This substantiated the clinical impression that all of the active thyroid tissue lay within the tongue.

Operation.—Under endotracheal ether anesthesia transverse incision was made in a cervical crease at the level of the hyoid bone (Fig. 1). The skin and subcutaneous tissues were elevated from the line of incision to the inferior border of the mandible, leaving the platysma in place to protect the intramandibular branches of the facial nerves. Through incisions along the anterior borders of the sternocleidomastoid muscles the external carotid arteries were exposed and a catgut loop was placed around each of them for traction. An incision was then made in the midline from the inferior border of the mandible to the hyoid bone, separating the mylohyoid, and at a deeper level, the geniohyoglossus muscles, thereby exposing a well-circumscribed mass which was about the size of an English walnut, completely enclosed within the posterior portion of the tongue (Fig. 2). Its superior surface was in contact with the dorsal mucous membrane of the tongue. The mass was quite vascular and had the appearance of thyroid tissue. Obstruction of the external carotid arteries produced ischemia of the mass and of the surrounding muscles. Thus it was possible to resect this vascular structure without bleeding and without contamination from the oral cavity. A thin plaque of thyroid tissue was left within the base of the tongue in order to prevent complete myxedema. It was realized this might result in recurrence of the lingual mass and the return of obstructive symptoms. The wound was closed in layers with interrupted sutures of 0000 silk. The skin sutures were removed after forty-eight hours and the patient left the hospital on the fourth postoperative day. Thyroid extract (4 gr. daily) has prevented the development of clinical myxedema. When this patient was last examined, three and one-half years postoperatively, there was no evidence of recurrence of the lingual goiter.

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Fig. 1.—Photograph showing inconspicuous cervical incision for exposure and removal of lingual goiter.

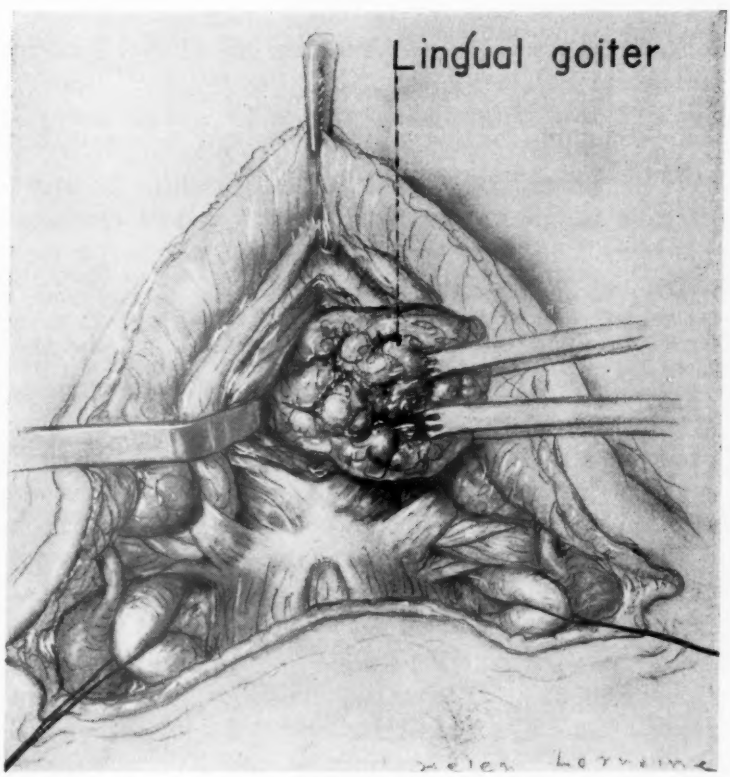

Fig. 2.—Drawing showing approach for exposure of a mass within the tongue and exposure of both external carotid arteries.

DISCUSSION

The cervical approach for excision of lingual goiter has been used occasionally since 1888 when Bernays[1] performed the operation through a suprahyoid midline incision. Of one hundred lingual thyroidectomies found in the literature, the cervical approach was used in thirty-nine while sixty-one were removed by the oral route.

Various incisions have been used for the external approach: vertical, transverse, T-shaped, U-shaped, and others. In a few instances the mandible was divided, while in others the hyoid bone was cut across. Tracheotomy has occasionally been necessary because of swelling of the tongue, but hemorrhage has been the most frequent complication. Because of the danger of hemorrhage a few surgeons have performed preliminary ligation of the lingual arteries, but unilateral ligation is not effective and bilateral ligation may result in poor healing or may even cause necrosis of that portion of the tongue adjacent to the incision. The technique herein described permits complete control of bleeding without the risk of poor healing or necrosis. The approach is anatomic and the resulting scar is inconspicuous. With adequate control of bleeding, minimum trauma, and avoidance of contamination with mouth organisms, complications such as hemorrhage, infection, and respiratory obstruction should be of rare occurrence. The preoperative use of irradiated iodine should make exploration for cervical thyroid tissue unnecessary.

SUMMARY

An anatomic technique for lingual thyroidectomy is presented which enables the surgeon to work in an aseptic and bloodless field.

REFERENCES

1. Bernays, A. C.: The Origin of the Foramen Coecum Linguae as Shown by an Operation on a Rare Tumor of the Root of the Tongue. A Preliminary Note, St. Louis M. & S. J. **55**: 201-205, 1888.
2. Nachman, Herman, Crawford, V., and Bigger, I. A.: Radioactive Iodine (I^{131}) in Diagnosis of Lingual Thyroid, J. A. M. A. **140**: 1152-1156, 1949.

Editorials

The Disadvantages of Ureterosigmoidostomy

IT HAS been said that ureterosigmoidostomy with cystectomy offers the only hope of increasing the rate of cure in early or superficial cancer of the bladder. This view ignores the fact, which surgeons are gradually coming to realize, that diversion of the urine into the bowel frequently yields poor results in terms of the comfort of the patients, and that it usually reduces longevity. While the literature contains a number of reports of survivals for as long as twenty to forty years after ureterosigmoidostomy for exstrophy of the bladder, there is ample reason to believe that these represent the exceptions that prove the rule rather than the average results.

Both Jewett and Flocks have shown that the more conservative methods of surgical management (segmental resection, electrocoagulation) of early or superficial cancer of the bladder yield about 75 per cent of symptom-free five-year survivals. Harvard and Thompson have recently traced 128 of 144 patients subjected to ureterosigmoidostomy for exstrophy of the bladder between five and thirty-five years earlier. The surgical mortality was 12.5 per cent, and 13.6 per cent more died during the first five years after operation, i.e., the five-year survival rate of children after ureterosigmoidostomy in the absence of malignant disease was 86.4 per cent, ignoring the surgical mortality. This is about 13 per cent worse than the expected mortality for 10-year-old white boys in the United States in 1945, a group with which those subjected to ureterosigmoidostomy for exstrophy may reasonably be compared; however, it is about 11 per cent better than the five-year survival rate for the conservative surgical treatment of early or superficial cancer of the bladder reported by Jewett and Flocks. The apparent advantage disappears if one makes allowance for the surgical mortality. This was 6.1 per cent in 954 cases of cancer of the bladder treated by conservative surgical methods in the literature between 1935 and 1952. Subtracting this from the five-year survival rate of Jewett and Flocks, we get 69.9 per cent. The literature shows that the surgical mortality of ureterosigmoidostomy and cystectomy for cancer of the bladder between 1939 and 1950 was 21.7 per cent in 703 cases. Subtracting this from the five-year survival rate for ureterosigmoidostomy alone, we get a predicted five-year survival for the radical treatment of early or superficial cancer of the bladder of 86.4 minus 21.7, or 64.7 per cent. Even this hypothetical figure makes no allowance for the greater postoperative mortality to be expected in old people and from the recurrences or metastases of malignant disease, as compared to that of young people treated for benign lesions such as exstrophy. It is evident, therefore, that the methods thus far available for diverting the urine into the bowel and removing

the bladder are not successful enough to justify their use for a disease in which conservative surgical methods yield 75 per cent of five-year survivals (or 69.9 per cent of those treated).

What causes the poor prognosis after diversion of the urine into the bowel? It is mainly the renal damage resulting from free communication between the kidneys and the infected contents of the colon. In addition, several factors usually operate after such operations to produce hydronephrosis which, in turn, aggravates the effects of infection upon the kidneys. The ureter must be mobilized for at least a short distance to permit its union with bowel, and this is inevitably associated with some damage to its extrinsic blood supply. While the intrinsic vascular tree is ordinarily adequate to prevent necrosis, the impaired vascularity undoubtedly aggravates the effects of the unavoidable infection and all too frequently leads to inflammatory edema and later to granulomata and fibrosis with secondary strictures. These facts, which have been verified both clinically and experimentally, make dangerous any form of implantation which leaves a segment of ureter protruding into the bowel. This particular danger can be reduced or perhaps eliminated by slitting one side of the terminal ureter for a short distance and making a "terminolateral" anastomosis between the ureter and the edges of a short incision in the mucosa of the colon. If the ureter is joined in this manner to the full thickness of the colon without a submuscular trough, as suggested by Nesbit, reflux of the intestinal contents into the ureter becomes a serious problem. Air pyelograms are seen not infrequently after the operation of Nesbit as well as after that of Cordonnier; Whisenand and Moore saw gas and feces issue under pressure from nephrostomy tubes inserted prior to such an operation.

This danger (reflux) may be reduced but not eliminated by combining the "mucosa to mucosa" anastomosis with the submuscular tunnel of Coffey, a fact verified in the dog by Riba, by Woodruff, Cooper, and Leadbetter, and by Weyrauch and Young. On the other hand, Baker and Miller have found that reflux ultimately occurs in the dog even when the fecal stream is diverted above the anastomosis by preliminary colostomy, and the normal ureteral orifices with their mechanism for preventing reflux are preserved by anastomosing a portion of the bladder to the bowel. They attribute this to the fact that the pressure of normal defecation is so much higher than that of normal urination, and advocate anastomosis of the ureters to the descending colon where, they say without presenting supporting evidence, the normal pressures are considerably lower than those in the rectosigmoid. They offer no solution to the problem of preserving the blood supply of the right ureter while bringing it over to the descending colon.

Infection of a kidney which is connected to the colon may occur in the absence of reflux, however. Hinman Senior laid the intact ureter of the dog into a submuscular trough in the colon without opening either organ; hydronephrosis and pyelonephritis developed, presumably by way of the ureteral lymphatics since there was no opening between the lumina of the ureter and bowel.

Another threat to the kidneys is found in the compression of the ureter by scar in the portion of the colon traversed by it. This is doubtless reduced, but is certainly not eliminated by the use before and after operation of antibiotics some of which, especially in suitable combinations, may even yield sterile cultures from the colon. Unfortunately this effect thus far is fleeting because of the rise in the resistance of the remaining bacteria. Baker and Miller have been able to reduce scarring in the dog's colon at the site of the implanted ureter by the use of cortisone during the stage of healing. If this can be done consistently in the human being it will constitute a very important contribution.

The frequency and importance of postoperative hydronephrosis and pyelonephritis are reflected in reports of follow-up studies of patients with ureterosigmoidostomy. Harvard and Thompson attributed 67.5 per cent of the late deaths in their series to renal disease of this type. Lapides found some degree of pyelonephritis in every human being and dog autopsied after ureterocolic anastomosis; G. G. Smith uncovered evidence of serious renal disease in 16 of 54 patients (29.6 per cent) studied postoperatively. In 258 patients subjected to urography six months or more after operation (205 from the literature and 53 from our clinic) only 31 per cent had normal-appearing kidneys. Since the vast majority of these patients were investigated within a year of operation, it is evident that the long-term outlook for the kidneys is gloomy indeed.

Additional evidence of the frequency and severity of renal damage after ureterosigmoidostomy is found in the statistics on postoperative hyperchloremic acidosis. While this phenomenon was reported in 1931 by Boyd and in 1940 by Jewett, Ferris and Odel first studied it on a large scale in 1950. They observed it in 79 per cent of 141 consecutive cases of ureterosigmoidostomy. Although there is ample evidence that it results primarily from absorption of the urinary chlorides from the colon, there is just as good reason to believe that it assumes serious significance only if the renal tubules are damaged seriously enough to interfere with the excretion of the chlorides, and perhaps of the other acid radicles normally excreted in the urine. Our own studies have shown that it occurs three times as often and causes symptoms ten times as often in the presence of gross impairment of the renal function as when the kidneys respond normally to the ordinary tests of function.

Whether the incidence and severity of postoperative renal disease can be reduced significantly or eliminated by methods presently available is debatable. There is one surgical technique of considerable promise which has certainly not had the trial that it merits. Mauclaire in 1895 and Kroenig in 1907 suggested dividing the colon above the connection with the ureters, closing the distal segment, and bringing the proximal loop out as a colostomy, thus providing a relatively clean reservoir for the urine. This method was never widely tried, presumably because of the disadvantages of a colostomy. However, if one considers the evil effects of the usual postoperative renal disease which results mainly from pyelonephritis, the disadvantages of colostomy become insignificant provided that its use will reduce substantially the usual postoperative renal infection. That this may be so is suggested by the experience of Boyce and Vest.

They made a preliminary terminal colostomy in a 9-year-old boy with exstrophy of the bladder. The distal loop was then irrigated for some time with suspensions of antibiotics before vesicosigmoidostomy (a modified Maydl operation) was performed. Nine months later the excretory urogram was normal, there was no hyperchloremic acidosis, and, probably for the first time in history, the urine was sterile. While one case proves nothing more than that strange things may happen, the method appears to be sufficiently promising to require a thorough trial before concluding that it is just another variant of ureteral transplantation. It is probably the use of colostomy rather than the type of ureteral anastomosis used by Boyce and Vest which is of importance in preventing infection of the kidneys.

Many other methods have been devised to meet these problems; limitation of space prevents more than the briefest consideration of their principles. They include the isolation of a loop of ileum or colon to receive the ureters; this loop has been connected to the outside either as a wet stoma draining into a bag of some kind or, as in the operation of Gilchrist, Riegel, and Merricks, through a loop of ileum permitting the use of the ileocecal valve to prevent leakage of urine from the isolated cecum and ascending colon between catheterizations. Such methods do not offer any advantages in terms of protection of the kidneys and are useful only in connection with pelvic evisceration, if that operation is ever really indicated.

In conclusion, it is *not* suggested that ureterosigmoidostomy be abandoned, but rather that its use be confined to those cases for which there is no better alternative procedure available. In the meantime efforts to find a method to save the kidneys from the perils of obstruction and infection should be intensified. It is no achievement to increase the "cure rate" of cancer by a method which in itself produces invalidism and shortens life expectancy quite apart from the dangers of local recurrence and metastasis of the original lesion.

—C. D. Creevy

Specialization Versus General Training*

THE emphasis of the last several decades on specialization, which has been attractive to medical students and young physicians because of a combination of intellectual stimulus, prestige, and financial reward, has resulted in a possibly imperfect distribution of physicians between specialism and general medical care. The consumers of medical services have expressed the instinctive need for a family doctor who will combine professional services with a priestly function. In the broad pattern of medicine as a whole, this need, justified by the normal emotional reactions of humanity, has been less adequately met than

*Read at the dinner meeting of the Texas Surgical Society, April 7, 1952, Houston, Texas.

before the advent of specialism. The extraordinary increases which specialism has made possible in therapeutic potentialities and, consequently, in the saving of lives is often ignored or forgotten. We need not seek to resolve the question whether medicine's great successes in the one field have balanced its relative failure in the other. Whatever a wise estimation of this balance may be, the result has been that pressures are now exerted by the profession itself for the rehabilitation of the family doctor. Such rehabilitation has been and will continue to be a wholesome interest of the profession; but, unfortunately, its reasonable aim has been clouded and confused by the revival of pressure for complete medical care under what should be an obsolete term, namely "general practice."

No surgeon will fail to recognize that general practice in the full sense is incompatible with the rendering of first rate surgical care. How many common ducts have been sacrificed by the occasional operator? How many cancers of the stomach have been diagnosed and radical operations denied because the surgeon lacked the training to undertake this procedure? How many operations for operable cancer of the breast are less than radical? No one knows, but these examples are common enough for us to cherish the ideal that no one not adequately trained in surgery should be permitted to be accepted by the public as worthy of its confidence as a surgeon. The steady growth of the resident training program, of the closed hospital staff, and of the certifying boards had led many of us to the conclusion that progress toward this ideal of surgery was being made. Now we know that this conclusion was complacent, that our satisfaction was illusory. The natural and justified demand for intimate and continuous medical care on the part of the public has served as an excuse for an attempt to tear down the painfully erected structure directed toward the fulfillment of our ideal, namely, to insure safe surgery to every unfortunate individual who must submit himself to operation.

Although not openly expressed, an idea can be readily obtained by inference from scattered statements that the pressure exerted in certain circles for the revival of "general practice" is motivated often by the desire of less than completely qualified men to assume the obligations and responsibility of surgery. Such a motive is concealed under definitions of adequate training that we as surgeons would not accept. Since many of these men do not know what proper training means in the development of knowledge of surgical disease in all its implications, of technical proficiency, of resourcefulness and of the ability to analyze and logically treat unusual or unexpected phenomena, one can often rather regret their ignorance than condemn their selfish lack of ideals. Envy directed toward the specialist is a natural emotion, which is harmful only to the man who is not stimulated thereby to the effort properly to qualify himself. One notes that many of these men forget their interest in operative privileges for the general practitioner when the need for operation comes close to home.

All this is familiar enough. What is this forceful movement going to mean to the immediate future of surgery? There are two possible results that may be presented briefly. The first has been touched upon. There are data on the number of operations performed daily, and hence an estimation is possible of

the number of operators needed. The number of needed operators must be identical with the number of trained surgeons. Whatever the total figures may be, saturation of the surgical field with trained surgeons is still in the future. The serious prospect is that the desired stamp of approval of the general practitioner as capable of surgery will mean that the percentage of operations performed by the untrained man will increase at the expense of the operations performed by the trained man. "Limited surgical privileges," a weasel phrase used as an entering wedge, means nothing. Dr. Hubert Royster's dictum will be remembered that there is no such thing as "minor surgery," stating the conviction that the simplest procedure may lead to the most perplexing or even the most grave consequences. The sick populace is where the inadequately trained general practitioner is going to learn his surgery, if he is capable of learning, at the expense of how many lives no one can know. In the earlier days when few had better opportunities for training, the neophyte probably learned his surgery more quickly than now simply because he was not facing the competition of young, well-trained surgeons and therefore could early expect more surgical patients among his clientele than the general practitioner can expect today. He may have learned it more quickly, but it may be wondered whether in that shorter time he was responsible for fewer unnecessary deaths. The failure to appreciate and properly to appraise this lesson of the past is one of the sadder commentaries on the tides of human progress.

The second aspect of the problem that I would present is the immediate effect that the emphasis in the medical schools on general practice will have on the conduct of our surgical services. The medical student of today has been bombarded with the information that there is a demand for family doctors, and has been presented with the emotional charms of this calling; he has not had pointed out to him that a demand also exists on quite as cogent grounds for increasing the number of adequately prepared surgeons. There have been offered to him many new opportunities for a supposedly rounded training in so-called rotating internships. So long as these do not include the assumption that a man can operate on his patients after the completion of a two-year rotating training period, there is no quarrel with them. The need for the family doctor is real, but he must be a "family doctor" and not a general practitioner. The result of this constant stimulation directed away from specialization in the technical branches of medicine is beginning to be evident. In my own school, two years ago, there was perhaps one-half of each graduating class that was interested in specialization. Now there are probably not more than twenty per cent. This change has already been reflected in the demand for surgical training. Straight surgical internships are often going begging.

In the higher grades of training, the same influence is clear. Part of this is undoubtedly due to the military situation; but there is doubt that all of it is. Demands for surgical training on the surgical service of the University of Virginia Hospital in the assistant residency grades ten years ago represented from four to eight times the places we could fill. Last year it was possible to fill the quota for this year only after some weeks of search. Whereas formerly

there was a rich field of candidates from whom we were able to pick superior men, today quantity rather than quality seems to be becoming the dominant problem. When we cannot choose our future residents from a varied field, it may be wondered what sort of leaders of house staff training we can look forward to a few years from now. I wonder, as a member of a teaching hospital staff, what quality of service we can exemplify to undergraduate medical students.

If we are to continue to uphold quality over quantity, another problem may quickly be posed. The organization of our surgical services leans heavily on the young man of the house staff. We delegate to him the details of patient care, from collecting blood samples to passing suction tubes and giving infusions and transfusions, time-consuming details which we believe are, within limits, valuable to his training and the delegation of which gives us the time for what we consider important aspects of our obligations. This delegation enables us to apply our more seasoned judgment to a greater number of clinical problems, to apply time to reading, to research, to the writing of papers, and to the administrative problems of hospital and medical school. It is true that many surgeons in smaller hospitals already carry the burdens of detailed patient care, and to them it can be said only that their preoccupation with these portions of the tasks that are necessary for the best surgical performance is regrettable. A situation that may result in relative inferiority of undergraduate teaching and of graduate surgical training is deplorable.

Finally, what are we to do about it? Certainly we cannot denigrate a movement in medicine of which in a qualified sense we all approve. We cannot say "there is no need for family doctors." We, on the other hand, are at once suspect of a selfish motive and therefore become ineffective protagonists if we preach too loudly the merits of our training programs. The one thing we must do is to bring to bear every influence we can upon the education of both the profession and the public toward recognition of the principle that the present propaganda for surgery by the untrained man is a degeneration of hardly won ideals and a very real danger to the health of the nation. If that concept can be firmly established, the problem of lack of interest in genuine surgical training can be expected to evaporate in time.

—*Edwin P. Lehman*

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

ANNULAR PANCREAS

REVIEW OF THE LITERATURE AND REPORT OF TWO INFANT CASES

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THE RARE developmental anomaly known as annular pancreas was given its name by Alexander Ecker,[23] who reported the first verified case of this unusual malformation in 1862. Most of the early cases were reported simply as interesting, incidental autopsy findings and few clinical data are available concerning many of these patients. However, with the passage of time and the development of improved methods of roentgenologic examination of the upper gastrointestinal tract, more patients have been studied clinically and verification of the diagnosis has been based frequently upon operative findings. Up to the present time, 68 cases of annular pancreas have been reported.[1-5, 7-38, 40-58, 60-64] This figure does not include the 3 cases, cited in McNaught's[37] 1933 summary (Tiedemann,[59] Becourt,[6] Moyse[39]), shown by Ravitch and Woods[46] to be conditions other than true annular pancreas, nor does it include the second case of Smetana,[51] which had previously been reported by Priesel.[45]

Recent interest in this problem, demonstrated by the report of 24 cases during the past 8 years, suggests that annular pancreas is perhaps not so uncommon as it was once thought to be. Symptoms associated with the presence of an annular pancreas generally do not appear until adult life. Acute duodenal obstruction has occurred, however, during the neonatal period in 6 cases.[13, 27, 30, 46, 62] Due to the limited number of cases described, it has been felt desirable to report 2 cases discovered in infancy and to review the pertinent literature.

CASE REPORTS

CASE 1.—The patient, a 7-week-old girl, was admitted to the hospital on April 2, 1944, because of convulsions of 4 days' duration. Her birth weight was 8 pounds, 1 ounce and the pregnancy had been normal. She had been bottle-fed and had taken the feedings well until the onset of convulsions. Her weight on admission was 10 pounds, 10 ounces and the temperature was 104° F., the hemoglobin 7.5 Gm., and the white blood count 14,000. The physical examination was essentially nonrevealing with the exception of a right otitis media. It responded satisfactorily to sulfadiazine with the return of the temperature and laboratory findings to normal levels within a few days. The patient,

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however, remained lethargic with occasional convulsions. Bilateral subdural taps demonstrated the presence of a right subdural hematoma. She died on May 23, at 3½ months of age, in peripheral vascular collapse 3 hours after a right craniotomy had been carried out for the treatment of her subdural hematoma. During the 7 weeks of hospital observation, the patient had taken her feedings well and had retained virtually all of them. On only 5 occasions during this period did she vomit and only twice was the regurgitation projectile. Her stool and urine output was normal and she progressively gained weight, weighing 13 pounds, 7 ounces at the time of death. There had been no history of jaundice and jaundice was not observed during the hospital course.

With the exception of the residual membranes of a right subdural hematoma, the principal findings of interest on post-mortem examination were limited to the peritoneal cavity. The second portion of the duodenum was encircled by an annular pancreas and there appeared, in addition, to be a degree of obstruction at the pylorus (Fig. 1, *A*). Section through the duodenum and pylorus showed considerable narrowing at the site of the annular pancreas as well as narrowing and elongation of the pyloric canal with some thickening of the pyloric musculature (Fig. 1, *B*). No other congenital malformations were encountered.

Comment.—The annular pancreas was an incidental and unsuspected post-mortem finding in this case, death resulting from subdural hematoma and post-craniotomy shock. From the degree of duodenal and pyloric narrowing discovered at necropsy, it is rather surprising that this patient was so free of obstructive symptoms. Had symptoms occurred, pyloromyotomy and duodeno-jejunostomy would appear to have been the preferable method of treatment.

CASE 2.—The patient, a 5-day-old female infant, was admitted to the hospital on June 11, 1949, because of jaundice and vomiting since birth. She had been born approximately 3 weeks prematurely and weighed 5 pounds, 13 ounces at birth. Delivery had been uncomplicated and there had been no history of Rh incompatability. The patient was said to have vomited all her feedings since birth. She was markedly dehydrated and acutely ill. Her temperature on admission was 104° F. and she weighed 4 pounds, 8 ounces. The skin was jaundiced with decreased turgor. The hemoglobin was 18 Gm., the red blood count 5.0 million and the white blood count 25,000. Roentgenographic examination at the time of admission to the hospital showed evidence of marked bilateral pneumonitis which was felt to be due to the tracheobronchial aspiration of vomitus. There was also radiologic evidence of marked gaseous dilatation of the stomach and the first portion of the duodenum. No gas could be seen elsewhere in the gastrointestinal tract beyond the point of duodenal obstruction. Clinically, it was felt that the patient was probably suffering from a combination of duodenal atresia and congenital atresia of the bile ducts. Surgical intervention was deemed unwise until the patient's severe dehydration had been corrected and her desperate general condition improved. She was placed in an oxygen-humidicrib and was given large doses of penicillin. Parenteral replacement of lost fluids and electrolytes was begun. The patient, however, failed to respond to these measures and died 14 hours after admission to the hospital.

Post-mortem examination was carried out. Numerous areas of pulmonary consolidation were encountered grossly. Histologic study of the areas of consolidation revealed the presence of large mononuclear phagocytes with foamy cytoplasm suggesting the aspiration of lipoid material. Approximately 50 c.c. of dark amber fluid were found on entering the peritoneal cavity. The stomach and the first portion of the duodenum were markedly dilated, primarily due to contained air. The pylorus appeared to be normal. There was a constriction at the site of the ampulla of Vater, in the second portion of the duodenum, produced grossly by an annular band of pancreatic tissue completely surrounding the duodenum (Fig. 2). The lumen of the duodenum at the site of constriction was markedly narrowed, measuring less than 1 mm. in diameter. The gall bladder was filled with dark

green bile. There was no evidence of biliary tract atresia. The liver was slightly enlarged. No evidence of intrahepatic biliary atresia was encountered on microscopic study. No other congenital malformations were found.

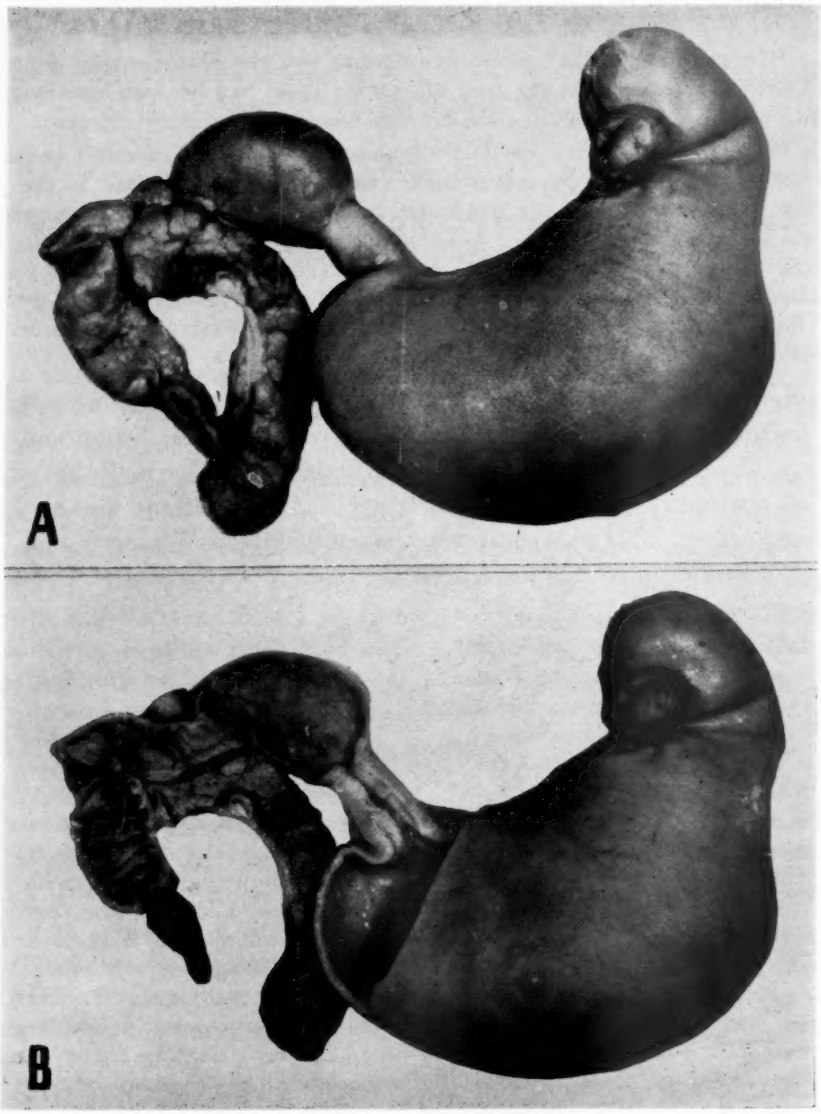

Fig. 1.—Photograph of necropsy specimen in Case 1 showing constriction of the second portion of the duodenum by an annular pancreas and narrowing of the pyloric canal by muscular hypertrophy before *(A)* and after *(B)* section.

Comment.—Death in this case resulted from excessive loss of fluids and electrolytes and aspiration bronchopneumonia secondary to unrelieved duodenal obstruction. The condition of this infant on admission to the hospital was obviously too poor to warrant surgical intervention at that time and she died a short time later, failing to respond to emergency replacement measures. From the degree of duodenal narrowing at the site of the annular pancreas, it is probable that congenital duodenal stenosis was associated with the pancreatic mal-

formation. It was quite apparent that simple division of the constricting pancreatic ring would have been ineffectual in this case. Rather, duodenojejunostomy would have been the ideal method of treatment for this patient. The jaundice was presumably obstructive in nature, resulting from constriction of the common bile duct by the annular pancreas at the ampulla of Vater. Pressure on the common bile duct by the dilated first portion of the duodenum may have been an added factor in the production of biliary tract obstruction. Cholecystenterostomy may be indicated in some cases to relieve biliary tract obstruction as well as to decrease the likelihood of regurgitant pancreatitis when the obstruction is at the ampulla of Vater.

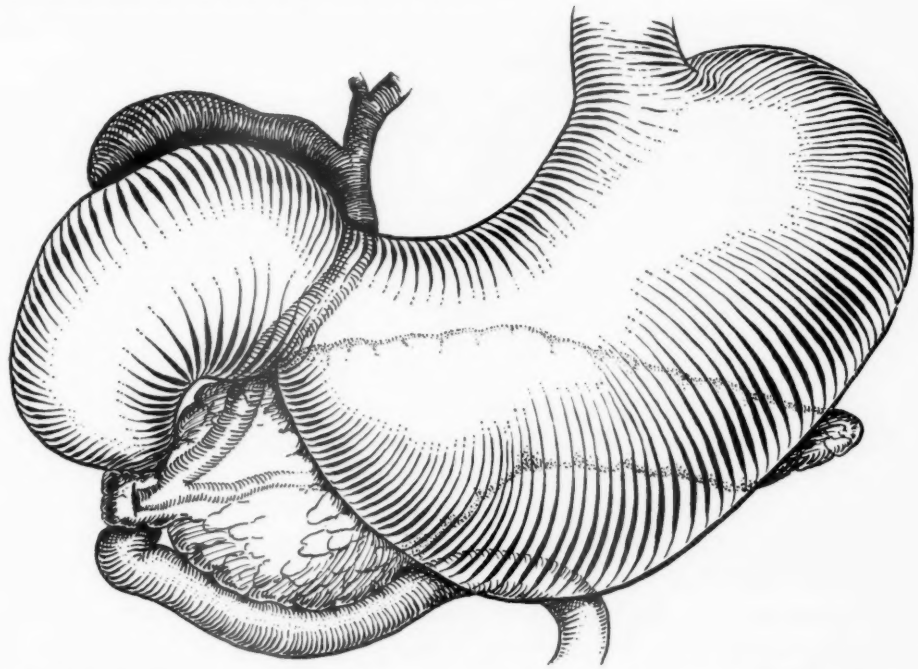

Fig. 2.—Diagrammatic portrayal of post-mortem findings in Case 2 showing duodenal and biliary tract obstruction from an annular pancreas at the ampulla of Vater.

Although there is no uniform opinion concerning the proper embryologic explanation of the occurrence of annular pancreas, most writers agree with the theory, originally advanced by Lecco,[34] that this anomaly results from a failure of the ventral anlage of the pancreas to rotate normally with the duodenum. This failure of rotation would leave the duodenum completely encircled by pancreatic tissue, with the duct of the ventral anlage arising in the pancreatic tissue on the anterior surface of the duodenum and coursing to the right and then posteriorly to join the main pancreatic duct, as is actually the case in most reported instances of annular pancreas. This theory, based on the meticulous study of the pancreatic duct system in 2 cases of annular pancreas by Lecco in 1910, was given added support by the publication of instances of incomplete ventral anlage rotation by Baldwin,[5] in 1910, and Bell,[7] in 1922. A few authors,[36, 60, 63] however, feel that annular pancreas arises simply as an overgrowth, or hyperplasia, of one of the pancreatic ducts.

The site of the opening of the duct of the annular portion of the pancreas was given in 19 of the recorded cases. The duct opened into the main pancreatic duct (Wirsung) in 16 cases and into the accessory pancreatic duct (Santorini), the common bile duct, and separately into the duodenum in 1 case each. The annular segment of the pancreas consists, microscopically, of normal-appearing pancreatic tissue. It should, perhaps, be emphasized at this point that annular pancreas and accessory pancreas are separate anomalous entities.

TABLE I. AGE DISTRIBUTION OF PATIENTS WITH ANNULAR PANCREAS*

AGE	NUMBER OF CASES
Fetus	3
0 to 10 days	7
10 days to 1 year	5
1 to 9 years	3
10 to 19 years	2
20 to 29 years	9
30 to 39 years	10
40 to 49 years	3
50 to 59 years	4
60 to 69 years	7
70 to 79 years	5
Total	58

*The exact age was not given in 5 additional cases beyond the statement that they were adults. Two were said to be aged.

Forty-five of the 61 patients whose sex was given were males (72 per cent). This unusual anomaly has been found to occur in both Negro and Oriental, as well as in white, patients. Although the age distribution in the reported cases has varied widely, ranging from a 16 mm. fetus[63] to 2 patients 74 years of age,[20, 51] the majority of the patients have been adults (Table I). Annular pancreas has been discovered, however, in the neonatal period due to acute duodenal obstruction in 7 cases, including the second case reported here. The ages of these patients have ranged from 3 to 8 days. Annular pancreas was also encountered in 5 older infants, between 1 and 8 months of age.[18, 27, 47, 51] Associated anomalies, at times multiple, were recorded as present in 18 cases (Table II).

Although the diagnosis of annular pancreas cannot be made with certainty without operative or post-mortem examination, the possible presence of this

TABLE II. ASSOCIATED ANOMALIES

Malrotation of the intestines	3
Duodenal atresia	2
Duodenal stenosis	1
Hypertrophic pyloric stenosis	1
Partial absence of pylorus	1
Aberrant pancreas	2
Imperforate anus	2
Meckel's diverticulum	2
Mental retardation	2
Portal vein anterior to duodenum	1
Diaphragmatic hernia	1
Horseshoe kidney	1
Aplasia of kidney and ureter	1
Clubfoot	1
Cleft palate	1

lesion should always be borne in mind in all cases with radiologic evidence of duodenal obstruction, particularly of the second portion of the duodenum.[35] Clinical disabilities resulting from the presence of an annular pancreas vary according to the age at which symptoms appear. Duodenal obstruction is the most consistent and dramatic symptom of annular pancreas in the neonatal period, whereas, in adulthood, the patient's complaints are often of vague and poorly defined epigastric distress and indigestion, resembling, at times, the symptomatology of peptic ulceration. The discomfort experienced by adults often comes on between meals and, in some cases, may be relieved by food or sodium bicarbonate. Occasionally an annular pancreas may be completely asymptomatic, being discovered simply as an incidental finding at autopsy.

The principal clinical findings associated with annular pancreas are duodenal obstruction, peptic ulceration, or inflammation of the stomach or duodenum, jaundice resulting from biliary tract obstruction, and pancreatitis. Acute duodenal obstruction was encountered principally during the first few days of life. Only 1 instance has been reported, by Benedetti,[8] of acute duodenal obstruction in an adult due to annular pancreas. In this case, the obstruction was caused by acute pancreatitis with marked swelling and edema of the annular portion of the pancreas. The finding of duodenal atresia or stenosis in 3[46, 62] of the 7 patients studied during the first postnatal week suggests that the incidence of coexistent intrinsic duodenal lesions may be relatively high in patients whose symptoms begin shortly after birth—giving added forcefulness to the arguments for the by-pass type of operation.

The existence of peptic ulceration of the stomach or proximal duodenum was verified in 6 adult cases.[4, 11, 15, 17, 20, 42] The operative specimen, in 1 additional case, showed evidence of severe acute gastritis.[41] The complaints of several other adult patients might possibly be explained by the presence of gastroduodenal inflammation and irritation—or pancreatitis. Since the annular pancreatic ring around the duodenum is, at times, proximal to the ampulla of Vater, it is possible that the neutralization of gastric acidity by the alkaline pancreatic and biliary secretions is impaired. Chronic duodenal distention and stasis contribute, no doubt, to this difficulty.

Jaundice was present in 3[13, 46] of the 7 neonatal cases, including the case reported here. It was presumably due to biliary tract obstruction from the constricting annular pancreas. Pressure on the common duct by the distended proximal duodenum might also have been a factor. Jaundice was reported in 2 of the 5 patients observed later in infancy. Reitano[47] described the presence of icterus and acholic stools in a male infant with annular pancreas who died at 5 months of age. Gross and Chisholm[27] mentioned a case of annular pancreas, studied at the Children's Hospital of Boston by Dr. Sidney Farber, in which the common duct was completely blocked. The patient was markedly icteric, with acholic stools, prior to death at 5 months of age. Three of the adult patients were also jaundiced.[2, 12, 37]

The carefully studied case of Anderson and Wapshaw[2] provides an excellent illustration of the features of jaundice in an adult due to an annular

pancreas. Their patient, a 32-year-old woman, was admitted to the hospital during an attack of upper abdominal pain with nausea, vomiting, and jaundice. The patient had had 2 similar episodes, 6 and 8 months prior to admission, and she had been jaundiced for several days during the second attack. Her stools were acholic. Five days after the patient entered the hospital, her jaundice disappeared. The gall bladder was found later, on cholecystography, to be nonfunctioning. On exploration, the cystic and common ducts were discovered to be considerably dilated. No stones were found in the gall bladder or ducts. Further exploration revealed the presence of an annular pancreas which completely encircled the second portion of the duodenum. The ring was firm, suggesting chronic inflammation. There was no apparent duodenal obstruction. A segment of the annular pancreatic ring was resected and microscopic study of the surgical specimen revealed evidence of chronic pancreatitis and fibrosis. The authors have included in their article an excellent reproduction of the findings on cholangiography, through a T tube in the common duct, 14 days postoperatively. The common duct remained quite large with an apparent obstruction at the distal end. Both the main and accessory pancreatic ducts were visualized. This case would seem to indicate that the hazards of residual biliary tract obstruction following division or resection of the pancreatic ring are as real as those reported of residual duodenal obstruction following this method of treatment.

The patient of Zech,[64] although not jaundiced, showed cholecystographic evidence of a marked delay in gall bladder emptying following a fatty meal, possibly due to partial obstruction of the common duct by the annular pancreas. It would appear that a by-pass type of operation, possibly cholecystenterostomy, should be considered in those cases in which the jaundice seems to be clinically significant and due to obstruction of the common duct by the pancreatic ring, rather than by a dilated proximal duodenum.

Pancreatitis and pancreatic fistula formation have been particularly troublesome complications. Their true incidence has been difficult to assess. Most of these patients have been adults. The interesting case of Benedetti has already been discussed. The first patient reported by Brines[10] died shortly after drainage for acute hemorrhagic pancreatitis, the annular pancreas being discovered on post-mortem examination. The incidence of pancreatitis and pancreatic fistula following direct surgical attack on the annular pancreas, in the form of division or resection of the ring, has been distressingly high.

The patient of dos Santos,[21] treated only by posterior gastroenterostomy, was found at autopsy to have chronic pancreatitis. It is possible that the ill-defined symptoms of epigastric discomfort reported so often in adult patients with annular pancreas may have been due to chronic pancreatitis in some cases. Had contemporary methods of serum amylase determination been available and utilized, the incidence of established pancreatitis might have been somewhat higher. The possibility that the pancreatitis may be of a regurgitant nature tempts one to speculate concerning the advisability of a by-pass type of operation to reduce biliary tract tension. The possible use of parasympathetic blocking by Banthine or vagotomy should also be borne in mind.

The first successful operation for annular pancreas (gastroenterostomy) was reported by Vidal[62] in 1905. Operations for the relief of the symptoms associated with annular pancreas have been carried out on 30 patients up to the present time. The methods used and the results are summarized in Table III. The results from division or resection of a portion of the pancreatic ring have generally been poor, both with respect to the formation of pancreatic fistula and to the persistence of evidence of duodenal or biliary tract obstruction. The reported experience with by-pass operations, especially duodenojejunostomy, has been more encouraging. Howard,[31] following an unhappy experience with pancreatic ring division, was the first to suggest duodenojejunostomy. He felt that it would provide better relief of duodenal stasis than gastrojejunostomy. Gross and Chisholm,[27] in 1944, were the first to report the successful use of duodenojejunostomy in a case of annular pancreas. Subsequent experience with this method has been published by Ravitch and Woods.[46]

Subtotal gastric resection with gastrojejunostomy has been carried out on 4 of the patients with accompanying gastric or duodenal ulcers. One potential risk in these cases would seem to be the increased danger of duodenal stump difficulty with an obstructing annular pancreas distal to the site of duodenal stump closure. Cattell[15] combined division of the pancreatic ring with gastrectomy and gastrojejunostomy. His patient developed a postoperative pancreatic fistula. Baker and Wilhelm[4] have reported the successful use of duodenojejunostomy with gastric resection and gastrojejunostomy. Although no experience with their combined use has as yet been published, vagotomy and gastrojejunostomy would seem to have some theoretical merit in these cases.

SUMMARY

1. Two cases of annular pancreas discovered in infancy are reported.
2. The literature pertaining to annular pancreas is reviewed.
   (a) Seventy cases of annular pancreas, including the cases recorded here, have been reported up to the present time.
   (b) Seventy-two per cent of the patients whose sex was given were males and the majority of the patients have been adults.
   (c) The principal associated clinical findings were: duodenal obstruction, peptic ulceration or inflammation of the stomach and proximal duodenum, jaundice from biliary tract obstruction, and pancreatitis.
   (d) Acute duodenal obstruction and jaundice were encountered more frequently in infants, while chronic duodenal obstruction, pancreatitis, and gastroduodenal ulceration occurred more often in adults.
   (e) Jaundice was present in 3 of the 7 patients studied during the neonatal period. Furthermore, 5 of the 12 patients whose annular pancreas was discovered during the first year of life were icteric. Three of the adult patients were also jaundiced.
   (f) The reported operative experience in 30 cases of annular pancreas is summarized.
   (g) Pancreatic fistula formation and residual obstruction, duodenal or biliary, have all too frequently accompanied division or partial re-

TABLE III. OPERATIVE MANAGEMENT OF REPORTED CASES OF ANNULAR PANCREAS*

OPERATION	NUMBER OF CASES	INFANT	ADULT	POSTOPERATIVE PANCREATITIS	POSTOPERATIVE PANCREATIC FISTULA	RESIDUAL DUODENAL OBSTRUCTION POSTOPERATIVELY	RELIEF OF OBSTRUCTIVE SYMPTOMS	DIED
Gastrojejunostomy[9, 11, 17, 21, 40, 51, 61, 62]	8	1	7	0	0	0	5	3
Subtotal gastrectomy[20, 41] and gastrojejunostomy	2	0	2	0	0	0	2	0
Subtotal gastrectomy,[4] gastrojejunostomy, and duodenojejunostomy	1	0	1	0	0	0	1	0
Subtotal gastrectomy,[15] gastrojejunostomy, and division of pancreatic ring	1	0	1	0	1	0	1	0
Subtotal gastrectomy and Billroth I (proximal) gastroduodenostomy[42]	1	0	1	0	0	1	0	0
Gastro-(distal)duodenostomy[46]	1	1	0	0	0	0	1	0
Duodenojejunostomy[27, 46]	3†	2	1†	0	0	0	3†	0
Division or partial resection of pancreatic ring[2, 12, 17, 26, 29, 31, 35, 36, 44, 46, 50]	11†	1	10†	2	3	6†	4	1
Division or resection of ring with Heineke-Mikulicz duodenoplasty[13, 22, 64]	3	1	2	0	2	1	1	1
Total	30†	6	24†	2	6	8†	18†	5

*The first case reported by Brines[10] is not included because only drainage of the peritoneal cavity was carried out. The annular pancreas was not discovered until post-mortem examination.

†One patient was treated initially by partial resection of the pancreatic ring. Because of persistent duodenal obstruction, duodenojejunostomy was later used successfully.[46]

section of the pancreatic ring. Sufficient experience with the hazards of this method of treatment has accumulated to regard it as inferior to the other available methods.

(h) The most satisfactory results have been obtained with the by-pass types of operation. Although the published experience with its use is as yet limited, duodenojejunostomy appears to be the most rational of these operations.

3. The suggestion is made that a by-pass type of operation such as cholecystenterostomy may be indicated in some carefully selected cases to relieve biliary tract obstruction.

4. The use of vagotomy as an adjunct to the by-pass management of the duodenal obstruction of annular pancreas in those cases with pancreatitis or gastroduodenal ulceration is perhaps worthy of consideration, especially when gastrojejunostomy is used.

ADDENDUM

Since this article was submitted for publication, reports of two additional cases, both treated operatively, have come to my attention. Glover and Hamann (Ohio State M. J. 36: 833, 1940) report their Case 20, that of a 5-week-old infant who was treated initially by division of the pancreatic ring. Gastrojejunostomy was carried out successfully a short time later because of residual duodenal obstruction. Wakeley (Lancet 2: 811, 1951) reports a 36-year-old man whose case was managed successfully by division of the pancreatic ring.

REFERENCES

1. Anderson, J. K.: Abnormalities of the Duodenum, Brit. J. Surg. 10: 316, 1923.
2. Anderson, J. R., and Wapshaw, H.: Annular Pancreas, Brit. J. Surg. 39: 43, 1951.
3. Auberg: Quoted by Ancelot, Étude sur les maladies du pancreas, Paris, 1866.
4. Baker, J. W., and Wilhelm, M. C.: Annular Pancreas, Gastroenterology 15: 454, 1950.
5. Baldwin, W. M.: A Specimen of Annular Pancreas, Anat. Rec. 4: 21, 299, 1910.
6. Becourt, G.: Recherches sur le pancreas, Strasbourg, 1830.
7. Bell, H. H.: Horizontal and Vertical Pancreas in Association With Other Developmental Abnormalities, Anat. Rec. 23: 315, 1922.
8. Benedetti, U.: Contribrito allo Studio del Pancreas annulare, Policlinico (sez. chir.) 27: 81, 1920.
9. Bickford, B. J., and Williamson, J. C. F. L.: Annular Pancreas, Brit. J. Surg. 39: 49, 1951.
10. Brines, O. A.: Annular Pancreas, Involved in Acute Hemorrhagic Pancreatitis, Ann. Surg. 92: 241, 1930.
11. Brines, O. A.: Annular Pancreas Associated with Peptic Ulcer, Am. J. Surg. 12: 483, 1931.
12. Brown, M., Bingham, D. L. C., and Cronk, L. B.: Annular Pancreas, Gastroenterology 11: 367, 1948.
13. Burger, R. E., and Alrich, E. M.: Annular Pancreas, South. Surgeon 15: 83, 1949.
14. Cartellieri, P.: Beitrag zur Lehre von den Zwerchfellsmissbildungen, Virchows Arch. f. path. Anat. 263: 599, 1927.
15. Cattell, R. B.: Discussion of paper by Payne, R. L., Jr., Ann. Surg. 133: 762, 1951.
16. Chapman, J. L., and Mossman, H. W.: Annular Pancreas, Am. J. Surg. 60: 286, 1943.
17. Conroy, C. F., and Woelfel, G. F.: Annular Pancreas, SURGERY 29: 209, 1951.
18. Cords, E.: Ein Fall von ringformigem Pankreas, Anat. Anz. 38: 33, 1911.
19. Cunningham, G. J.: Annular Pancreas, Brit. J. Surg. 27: 678, 1940.
20. Custer, M. D., Jr., and Waugh, J. M.: Annular Pancreas With Secondary Dilatation of the Duodenum, Proc. Staff Meet., Mayo Clin. 19: 388, 1944.
21. Dos Santos, R.: Deux lesions rare du duodenum, XV Congres International de Medecine, Lisbon, 9: 419, 1906.
22. Dubost, C., Allary, M., and Sullivan, M.: Un cas de pancreas annulaire, Rev. de chir., Paris 69: 379, 1950.
23. Ecker, A.: Ztschr. f. rat. Med. 14: 354, 1862.

24. Ehlers, H. W. E.: Ueber ein Pancreas annulare bei gleichzeitig besthender offenbar angeborener Erweiterung der intra-und extrahepatischen Gallengange und des Pankreasganges, Beitr. z. path. Anat. u. z. allg. Path. **84:** 529, 1930.
25. Genersich, A.: Seltene Anomalie des Pankreas (ringformige) Umschliessung des Duodenums mit Verengerung desselben und consecutiver Magenerweiterung, Verhandl. d. X Internat. Med. Cong., 1890, Berlin, **2:** 140, 1891.
26. Goldyne, A. J., and Carlson, E.: Annular Pancreas Causing Duodenal Obstruction, Am. J. Surg. **71:** 429, 1946.
27. Gross, R. E., and Chisolm, T. C.: Annular Pancreas Producing Duodenal Obstruction, Ann. Surg. **119:** 759, 1944.
28. Gruber, B.: Ueber das Ringpankreas, München med. Wchnschr. **67:** 676, 1920.
29. Haden, W. D., Jr.: Annular Pancreas, Radiology **55:** 859, 1950.
30. Hennes, P.: Ueber angeborene Darmverengungen (Stenosen), Virchows Arch. f. path. Anat. **270:** 764, 1929.
31. Howard, N. J.: Annular Pancreas, Surg., Gynec. & Obst. **50:** 533, 1930.
32. Keyl, R.: Ein Fall von Ringpankreas, Anat. Anz. **58:** 209, 1924.
33. Kurozawa, S.: Mitt. d. med. Gesellsch. zu Tokyo **36:** 10, 1923.
34. Lecco, T. M.: Sur Morphologie des Pancreas Annulare, Sitzungsb. d. Wien, Akad. d. Wissensch. **119:** 391, 1910.
35. Lehman, E. P.: Annular Pancreas as a Clinical Problem, Ann. Surg. **115:** 574, 1942.
36. Lerat, P.: Contribution chirurgicale a l'etude du pancreas annulaire, Bull, Acad. roy. de méd. de Belgique, 4th Ser., **24:** 290, 1910.
37. McNaught, J. B.: Annular Pancreas, Am. J. M. Sc. **185:** 249, 1933.
38. McNaught, J. B., and Cox, A. J.: Annular Pancreas; Report of a Case With a Simple Method for Visualizing the Duct System, Am. J. Path. **11:** 179, 1935.
39. Moyse, D.: Etude historique et critique sur le pancreas, Thèse de Paris (No. 170, V. 530) 1852.
40. Nedelec: Stenose duodenale par malformation pancreatique congenitale sur D^2, intervention, Mém. Acad. de chir. **72:** 315, 1946.
41. Ohlmacher, A. P., and Marshall, E. A.: Annular Pancreas, Am. J. Surg. **79:** 473, 1950.
42. Orts Llorca, F., and Duenas Barrios, A.: Ulcus duodenal y pancreas anular, Rev. clín. españ. **36:** 407, 1950.
43. Ott, E.: Ueber die ringformige Umschnurung des Duodenums durch Pankreasgewebe, Inaug. Diss. Munchen, 1909.
44. Payne, R. L., Jr.: Annular Pancreas, Ann. Surg. **133:** 754, 1951.
45. Priesel, A.: Funf Falle von Bildungsanomalien des Pankreas, Wien, klin. Wchnschr. **36:** 407, 1923.
46. Ravitch, M. M., and Woods, A. C., Jr.: Annular Pancreas, Ann. Surg. **132:** 1116, 1950.
47. Reitano, R.: Sul pancreas anulare, Arch. ital. di anat. e istol. pat. **3:** 755, 1932.
48. Sandras, L.: Contribution a l'etude de la topographie et de la chirurgie du pancreas, These de Lyon. No. 37, 1897.
49. Shibata, I.: Tokyo med. Wchnschr. p. 2368, 1924.
50. Silvis, R. S.: Annular Pancreas, Ann. Surg. **135:** 278, 1952.
51. Smetana, H.: Ein Beitrag Zur Kenntnis der Missbildungen des Pancreas, Beitr. z. path. Anat. u. z. allg. Path. **80:** 239, 1928.
52. Stofer, B. E.: Annular Pancreas, Am. J. M. Sc. **207:** 430, 1944.
53. Sugawara, K., and Shibata, I.: Folia Anat. Tokyo. **3:** 239, 1925.
54. Summa, H.: J. A. M. A. **35:** 43, 1900.
55. Susukida, H.: Tokyo med. Wchnschr., p. 2396, 1924.
56. Symington, J.: Note on a Rare Abnormality of the Pancreas, J. Anat. & Physiol. **19:** 292, 1885.
57. Thacher, J. S.: Accessory Liver and Pancreas, Med. Rec. **44:** 152, 1893.
58. Thur, W.: Zur Kenntnis des Pankreas annulare, Wien. klin. Wchnschr. **42:** 444, 1929.
59. Tiedemann, F.: Ueber die Verschiedenheiten des Ausfuhrungsgangs der Bauchspeicheldruse beidem Menschen und den Saugethieren, Deutsch. Arch. f. Physiol. (Meckel), **4:** 403, 1818.
60. Tieken, T.: Annular Pancreas, Tr. Chicago Path. Soc. **4:** 180, 1899-1901. (also Am. Med. **2:** 826, 1901.)
61. Truelsen, F.: Annular Pancreas, Nordisk Med. (Hospitalstid) **6:** 2226, 1940.
62. Vidal, E.: Quelques cas de chirurgie pancreatique, Proces-Verbal Assoc. franc. chir. **18:** 739, 1905.
63. Weissberg, H.: Ein Pancreas annulare bei einem menschlichen Embryo von 16 m.m. lange, Anat. Anz. **79:** 296, 1935.
64. Zech, R. L.: Anomalous Pancreas as a Cause of Chronic Duodenal Obstruction, West. J. Surg. **39:** 917, 1931.

A REVIEW OF SOME RECENT ADVANCES IN THE STUDY OF SHOCK

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DURING the past thirty years, concepts of the reaction of the body to trauma have varied widely. In order to appreciate the present status of our thinking in this regard, it is necessary to know something of the experimental and clinical investigation that was done during World War I, when such great interest was shown in the nature, development, and treatment of wound shock.

Cannon's[1] work on hemorrhagic and wound shock during and shortly after World War I is now a classic. He showed that animals whose limbs had been traumatized would not develop shock if a tourniquet was left in place proximal to the damaged tissue. As soon as the tourniquet was released, however, the animal began to develop all of the signs of shock. He concluded that a toxic material was formed or liberated at the site of injury and that upon release of the tourniquet it circulated in the body, causing the toxic manifestation of shock. He further concluded that this toxic material was similar to, but not quite the same as, histamine, and therefore called it an H-substance.

During the decades following World War I certain investigators threw serious doubt as to the validity of this toxic theory of shock development. Blalock[2, 3] and, at about the same time, Parsons and Phemister[4] demonstrated that following tissue trauma there was a tremendous outpouring of blood and fluid into the extravascular space of the damaged tissue. Their work showed that an extremity traumatized in a manner similar to those in Cannon's experiments would swell in size following injury and that an appreciable amount of the circulatory blood volume would be lost into the damaged tissue. They concluded that such traumatic shock was due to a diminished circulating blood volume caused by extravasation and bleeding at the site of injury.

The clinical corollary of such experimental work naturally led to emphasis upon the replacement of circulating blood volume in shocked patients. Clinicians are all aware that this in turn resulted in the use of electrolyte solutions, plasma, and whole blood in the treatment of shock in an effort to replenish a depleted circulating blood volume.

During World War II, largely through the clinical observations and writing of surgeons from the Mediterranean Theater of Operations, whole blood was found to be far superior to other intravenous solutions in the management of shocked patients.[5, 6] The reason for the superiority of whole blood was felt to be due to its obvious ability to increase oxygenation of the tissues, as well as its more permanent effect upon keeping the vascular bed filled. Recently Moore[7] has pointed out another advantage of whole blood transfusions in filling

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the intravascular space, by emphasizing the tremendous size of the red cell mass compared to the other molecules that we might add to fill up the vascular tree. The size of a red cell in proportion to an albumin molecule, for example, is that of a large football stadium to a rowboat oar. It is obvious that in attempting to fill the intravascular space the red cell is the more effective substance.

At the moment the early use of whole blood in large amounts is without doubt the keystone of the management of the shocked patient. The relative advantages of using the intra-arterial route over that of intravenous administration is still under active consideration, but in the deeply shocked patient arterial administration seems to have some advantages.[8]

TYPES OF SHOCK

Although many efforts have been made to categorize various types of shock, no hard and fast definitions seemingly can be made. Clinical definitions are notoriously inaccurate reflections of the underlying physiologic state; in a like manner, the clinical situation that one person considers shock may not agree with the condition as understood by another. For example, some workers believe that marked hypotension must be present before shock can exist. Others point out that hypotension is only a late manifestation of the underlying pathology. Grant and Reeve[9] have attempted to classify shock according to such signs as warm hypotension, cold hypotension, warm tachycardia, and cold tachycardia. Needless to say, there is no general agreement concerning such classification.

Experimentally shock has been produced in many ways, resulting in a variety of types of shock, and often accounting for divergent findings. The aim of most of this work has been to set up conditions which are reproducible in a large series of animals and which are uninfluenced by extraneous stimuli. Experimental shock is ordinarily produced either by pure hemorrhage or by the result of tissue trauma.

Fine and his co-workers[10] have devised an apparatus producing pure hemorrhagic shock that provides for graded hemorrhage to any desired level of blood pressure (or percentage reduction in blood volume). The animal can be maintained for prolonged periods at such levels with the shed blood connected in a reservoir to the intravenous system. They have shown that after a prolonged period of hypotension such shocked animals will display a relaxation of the peripheral vascular tree and will take up the blood previously shed. This device is admirably suited to the study of pure hemorrhagic shock.

Traumatic shock has been reproduced by damaging the extremities of animals or by leaving a tourniquet in place for prolonged periods. A more exact method, however, has been devised by Noble and Collip[11] who place animals inside of a revolving drum containing a number of flanges. As the drum turns the animal is lifted to the top and then dropped to the bottom. The number of such measured falls depends on the revolutions per minute and the length of time the animal is left in the apparatus. In this way the amount of trauma is measurable and reproducible.

One of the interesting results of this ingenious apparatus is the fact that animals develop a type of resistance to injury so that they can withstand amounts of trauma that previously would have been fatal. Such animals develop a type of tolerance, resistance, or even immunity to shock.[12]

Although experimentally traumatic and hemorrhagic shock are produced in different ways, their fundamental pathology and pathogenesis are quite similar. In the case of hemorrhage, intravascular fluid is completely lost from the body. In traumatic shock, however, fluid passes from the intravascular space to the extravascular compartment at the site of trauma. Both produce a decreased intravascular volume despite the difference in fate of the fluid lost to the body economy.

Clinically the problem is obviously vastly more complex, for seldom do we see pure hemorrhagic shock. Usually the injured patient not only suffers the loss of blood externally and the passage of fluid into the injured member, but suffers pain, anxiety, extremes of temperature, tissue maceration (and the possible subsequent release of toxic materials), as well as the influence of all sorts of drugs and medications that those in charge may see fit to administer. It is no wonder, therefore, that categorizing clinical shock is a complicated and still unsettled problem.

THE ROLE OF PERIPHERAL VASCULAR TREE IN THE RESPONSE TO SHOCK AND BLOOD LOSS

For many years it has been recognized that the peripheral vascular network of vessels has a definite response to blood loss, trauma, and shock. In general, it has been known that these vessels constrict as the circulating blood volume diminishes, thus maintaining the effective circulating volume and sending the blood to more vital centripetal centers such as the brain and heart. Recently, however, this mechanism has been studied in detail and its mode of action more thoroughly understood, although there are still many important voids in our knowledge.

Zweifach and Chambers,[13, 14] by studying the exteriorized rat mesoappendix and the dog omentum in anesthetized preparations, have added greatly to our understanding of the architecture of the peripheral blood vessels. They have shown that under normal conditions blood passing through the small arterioles enters via a smaller metarteriole into a so-called preferential channel. From this usual thoroughfare numerous side channels lead into the capillary bed. The vessels so far described (the arterioles and the metarteriole) make up the first part of the preferential channel and are all surrounded by circumferential smooth muscle. Similarly the capillaries that branch from the metarteriole are protected at their openings by precapillary smooth muscle sphincters. These sphincters consist of a short cuff of smooth muscle, that upon contraction can close off the lumen of the capillaries or upon relaxation can reduce resistance and divert blood to that particular part of the capillary bed. The true capillaries which branch from the precapillary sphincters are endothelial-lined vessels which do not have a surrounding musculature.

The action of the vascular units described has been carefully noted under a variety of conditions, again using the intact rat mesoappendix as the source of study. Under normal basal conditions a vast majority of the capillaries are empty, the blood passing along the preferential channel past the tightly closed precapillary sphincters. Blood flows through some of the capillaries, but as time goes on first one and then another of these capillaries is shut off from the metarteriole as other capillary channels are opened. The musculature surrounding the arteriole and the metarteriole undergoes a rhythmic contraction which Zwiefach and Chambers have called vasomotion. This periodic contraction and relaxation apparently is not related to autonomic nervous system control, but is effected only by local humoral and tissue changes. Whatever the control, it is obvious that increased vasomotion and action of the precapillary sphincters control blood flow into the capillaries and have an all-important effect on blood flow and blood pressure. Indeed that is the essence of what has been formerly referred to as peripheral vascular tone.

The humoral control of vasomotion was investigated by studying the same exteriorized rat mesoappendix. First the preparation was studied in order to determine the smallest amount of epinephrine that would result in constriction of the precapillary sphincters. Then, by bleeding the animal or otherwise putting it in a state of stress, it was noted that the sphincters would at times be more sensitive to epinephrine, while at other times they would be less sensitive to the constricting substance.[15] Chambers and his co-workers[15] called the substance that enhanced the sensitivity to epinephrine vaso excitor material (VEM) while they termed the material acting in the opposite manner vaso depressor material or VDM.

A large amount of work has been done to determine the exact nature of these substances. The vaso excitor material (VEM) is apparently produced in the anoxic kidney and is destroyed or inactivated in the well-oxygenated kidney, brain, and liver. VDM, on the other hand, is produced in the anoxic liver and, to a small extent, in the anoxic muscle. This vaso depressor material is inactivated in the anaerobic or healthy liver, and is partially excreted in the urine.[16] Recent chemical studies[17] have suggested that VDM is the iron-containing protein, ferritin, and is only active when the sulfur-containing groups are in the Sulfhydral forms as opposed to the disulfide state (see Fig. 1).

The action of these substances has been carefully studied during various stages of hemorrhage and shock. In general two periods of activity have been described following hemorrhage. The first is characterized by a progressive vasoconstriction of peripheral blood vessels. Starting with the capillaries in the skin, this accounts for the pallor noted clinically. As hemorrhage continues, other nonvital structures suffer vasoconstriction and a subsequent reduction in capillary blood supply. Progressively this occurs in the skin, striated muscle, gastrointestinal tract, the kidney, and finally the liver. From a teleologic standpoint we can consider that less important organs give us their blood so that more vital organs may carry on.

During this phase of vasoconstriction the vascular tree is adapting itself to the progressively decreasing circulating fluid volume. Finally even larger arteries and veins may constrict to almost one-half of their normal diameter.

During this phase of the body's response to hemorrhage, Zweifach and others[18] have found evidence of the preponderance of circulating vaso excitor material. They describe its gradual appearance in the experimental animal as bleeding progresses, a situation in keeping with its alleged production in the anoxic kidney.

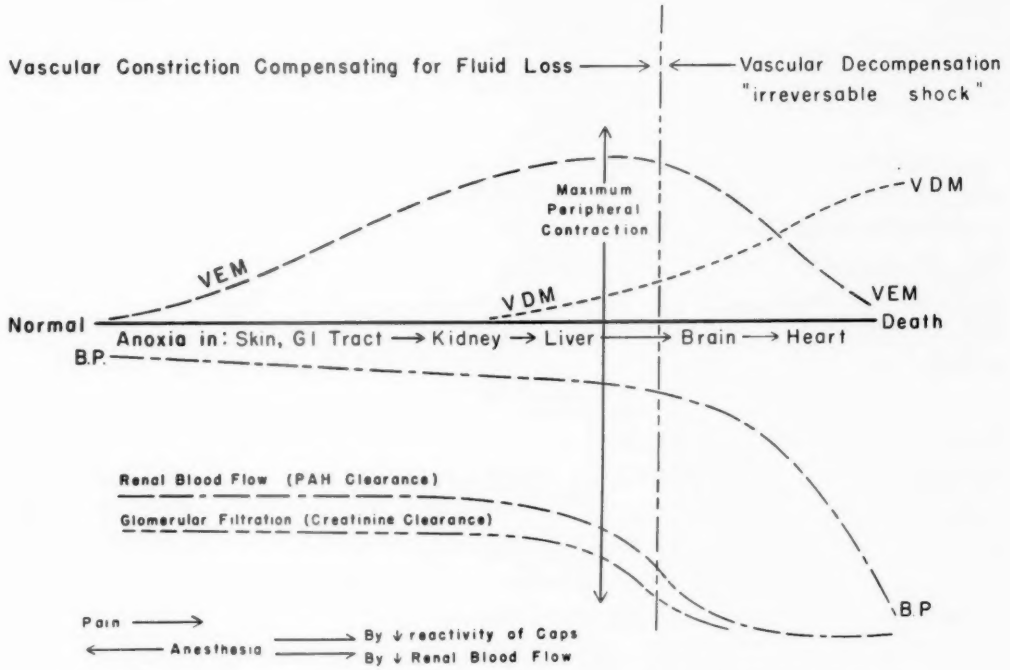

Fig. 1.—Progression of compensatory reactions in the development of shock.

It is well to note that during this period of vasoconstriction the vascular tree is compensating for the blood and fluid loss, and, since no discrepancy exists between the circulating blood mass and the containing system, the blood pressure by and large will remain unchanged, despite the systematic progression of serious underlying changes. Clinically it is well to keep this in mind, for we must realize that a normal blood pressure may be maintained and will not necessarily reflect the true physiologic state of the patient.

Kidney function and blood supply have been carefully studied during the progression of vascular compensation accompanying hemorrhage and shock.[19, 20] As hemorrhage continues major changes occur in the kidney. At first renal blood flow as measured by PAH clearance remains relatively normal, as other less vital structures suffer vasoconstriction. As hemorrhage continues, however, and despite a normal blood pressure, the kidney, along with other organs, begins to suffer a diminished blood supply and urine formation decreases. Finally, on further demand for vasoconstriction by continued bleeding, the kidney, too, suffers a decrease in blood supply to a point where urine formation and plasma clearances cease. This kidney debacle,[20] as Dr. Van Slyke has termed it, takes place when the peripheral blood pressure may still be within

normal limits. It is well to note that even when the kidney has been deprived of all except the bare minimum of blood supply that the liver remains relatively well vascularized—an organ protected long after the less vital kidney.

The second phase of reaction to hemorrhage has been called that of vascular decompensation. At some point in the progression of shock the blood vessels reach maximal vasconstriction, and despite further bleeding or stimulus no further contraction of the vascular space can take place. At this point almost all of the circulating blood is going to the heart, brain, and other absolutely vital structures in order to maintain life. Renal blood flow has stopped; urine formation has long since ceased; even the liver becomes anoxic. What then happens when further bleeding or trauma occurs? The ensuing condition has been called "irreversible shock" due to the difficulty or impossibility of revival when shock is carried beyond this point. It would seem that this is an unfortunate term, for it implies hopelessness and no need for further therapeutic effort. It is true that it may appear a more or less irreversible situation with our present state of knowledge, and with our present therapeutic methods, but who can say but that this dangerous border line may be altered by new methods of therapy.

Clinically at this stage of vascular decompensation shock deepens markedly. Blood pressure will fall sharply, the heart rate will become rapid in an effort to make the diminished blood volume serve all vital functions, heart sounds will become distant, and the pulse feeble. If allowed to progress, death will ensue.

Correlated with this decompensating phase of shock we find the predominance of the second circulating hormonal factor according to Zweifach and his co-workers.[21] The vaso depressor material, it will be remembered, is mainly produced in the anoxic liver, and as the hepatic blood supply is diminished there is a concomitant rise of circulating VDM. During the latter stage of the compensatory phase of reaction, the small amount of VDM produced is overshadowed by the relatively larger amounts of antagonizing VEM. As hemorrhage progresses, however, the VDM effect predominates, resulting in peripheral vascular dilatation or decompensation.

The proponents of the VEM, VDM theories of shock have hypothesized that vascular decompensation occurs because of the preponderance of the dilatory circulating hormone (VDM). Vasomotion (the rhythmic contraction of the circular smooth muscle of the terminal arterioles and metarterioles) decreases, and with it a decrease in peripheral vascular resistance. This, in turn, lowers the blood pressure. Of greatest importance, perhaps, is the relaxation of the precapillary sphincters, allowing blood previously dammed up in the main arterioles to pour into the hugh capillary bed, from which there is no force available to return it to the general circulation. Such sludged blood[22] is sequestered from the body economy and produces even more profound shock, and finally death. The progression of events in the development of shock is diagrammatically represented in Fig. 1.

So ends the progression of untreated progressive shock. It is obvious that we have not discussed the all-important part played by the endocrine system and particularly the role of the adrenal cortex. Mention likewise has not been

made of the importance of fluid transfer from the extravascular to the intravascular space. These are subjects in themselves, and are not within the scope of this review.

THE INFLUENCE OF PAIN, SEDATION, AND ANESTHESIA ON THE DEVELOPMENT OF SHOCK

The control of pain following trauma has quite naturally been an integral part of the management of the injured since early time. The exact effect of pain and the drugs relieving it have recently been carefully evaluated in relation to their effect on the shocked patient.

That severe pain has a deleterious effect upon the physiologic response of an injured patient is suggested by both experimental and clinical data. Overman and Wang[23, 24] bled a series of animals until 30 per cent to 40 per cent of their blood volume had been removed. They found that 50 per cent of such unanesthetized animals died of shock. When, however, under the same circumstances major afferent nerves were stimulated, producing pain, only a small percentage of their animals survived. It is clear that pain adds to the body's burden in shock and its relief will be of importance in resuscitation.

For many years it has been standard procedure to administer morphine almost as a routine to all severely injured patients. Beecher,[6] however, has pointed out that by no means all severely injured patients complain of, or even mention, pain as of serious consequence. Work originally begun on the Anzio Beach Head has been confirmed in Korea during the Hungnam-Hamhung evacuation. He has shown that intramuscular morphine given to a shocked individual may not be mobilized because of peripheral vascular collapse. Not until the individual is resuscitated will the accumulation of administered drugs be mobilized and then evidence of morphine poisoning or overdosage not infrequently develops.[25] His plea is to use restraint in sedating the injured and shocked patient.

Morphine, sedatives, and anesthetic agents not only may be unnecessary in the management of the injured, but it can be shown that such drugs actually further reduce the body's ability to compensate for blood and fluid loss. By anesthetizing the neural response of the peripheral vascular tree the constrictor response is diminished and the body is thereby less able to compensate for a decreasing blood volume. Gregersen[25] and his group have shown that morphine, for example, will decrease the respiratory rate and volume, decrease oxygen consumption, and will lower the blood pressure in animals in shock—conditions obviously not designed to aid in recovery.

In summary, therefore, pain has a deleterious effect upon the shocked individual, and when present must be controlled. Experience shows that it can be controlled on occasion with relatively smaller amounts of sedative than previously thought possible. Morphine and other sedatives and analgesics must be recognized as deleteriously affecting the body's response to a diminishing blood volume and, therefore, should be used with caution in shocked individuals.

THE ROLE OF BACTERIAL INFECTION IN THE PRODUCTION OF SHOCK

Bacterial infection can influence the production of shock in two separate ways: First, as Altemeier[26] has indicated in a short but comprehensive review, bacteria can be the actual cause of shock. Second, it appears that bacteria can markedly influence the progression of shock once trauma or hemorrhage has initiated the process. It is well to consider these two distinct roles separately, the former having been studied for at least 100 years, the importance of the latter having been recognized much more recently.

The action of bacteria or their metabolic products in the etiology of shock may be classified as follows[26]:

1. By decreasing the blood volume
2. By increasing the size of the vascular bed
3. By a direct toxic action on the heart
4. By interfering with the oxygen exchange mechanism of the red blood cell.

Decrease in blood volume results quite naturally from bacterial infections resulting in vomiting or diarrhea (Salmonella and other enteric infections) where large amounts of fluid are lost from the body. More acute intravascular fluid loss may result from massive exudation due to bacterial infection, such as occurs in pneumococcal pneumonia. The amount of fluid escaping into the alveoli of the lungs and thus lost to the circulating blood volume can partially account for the shocklike state that often results.[27, 28] In generalized peritonitis, within a relatively short period of time large amounts of fluid may be lost into the extravascular space of the peritoneal cavity, thereby contributing to shock.

Fluid transfer from the intravascular to the extravascular space takes place at any site of tissue trauma, but, when infection by *Clostridium welchii* or *Clostridium novyi* supervenes, such an outpouring of fluid is particularly characteristic. This fluid loss no doubt is one of the etiologic factors in the shock that so often accompanies such anaerobic infection.

The second method of shock production by bacterial action is through the increase in the size of the vascular bed, often with a normal or near normal circulating blood volume.

Such vascular dilatation may be due either to direct action of the bacterial toxins themselves or may result from the degradation products of tissues damaged by bacteria. As early as 1907, Janeway[29] reported vasomotor paralysis, and the passage of fluid out of the capillaries when certain bacteria and bacterial toxins were injected into animals. Vasomotor paralysis, capillary stasis, and peripheral vascular collapse may be found, for example, in severe pneumococcal infections and in typhoid fever, both clinically and when studied under experimental conditions. In a purer form this toxic action upon peripheral capillary walls has been studied by using the alpha toxin of *Clostridium welchii* and a similar toxin obtained from the hemolytic Streptococcus. Obviously the passage of fluid from the intravascular to the extravascular space, if severe enough, will contribute to a diminished effective circulating blood volume and, therefore, to the development of shock.

The role that tissue breakdown products play in the production of shock has been long debated[30] and several types of toxic material obtained from necrotic tissues have been implicated, ranging from the histamine to polypeptides and other types of protein degradation products. Bacteria initiate tissue necrosis in several ways and, therefore, may contribute to the liberation of such toxins. Hemolytic *Staphylococcus aureus* and anaerobic Streptococcus, for example, destroy tissue directly by means of necrotizing toxins, which are a product of their metabolism. On the other hand, a group of bacteria secrete enzymes which also results in tissue breakdown and the possible release of shock-producing toxins. In this group are included *Bacillus proteus, Bacillus pyocyaneus, Escherichia coli,* and several of the Clostridia, including histolyticum and sporogenes.

Other bacteria may cause tissue necrosis indirectly by thrombosing the vessels supplying the part involved with resultant tissue ischemia. Hemolytic *Staphylococcus aureus* and *Clostridium welchii* both may contribute to the tissue necrosis and, therefore, vascular collapse in this manner.

A third type of bacterial action in the production of shock results from direct myocardial damage by bacterial exotoxins. One of the best known of such actions is the myocardial weakness caused by diphtheria where cardiac output is markedly diminished.

Finally, it is now recognized that many bacteria interfere with the hemoglobin-oxygen exchange system directly, thus resulting in tissue anoxia and subsequent shock. The most obvious such mechanism is that of simple hemolysis with resulting anemia that can result from hemolytic Streptococcus infection. A more subtle, but equally lethal mechanism, is the direct interference with the hemoglobin molecule itself. Table I shows such mechanisms in outline form and demonstrates the wide variety of effects that bacteria can have on the oxygen-carrying properties of hemoglobin. In light of our present knowledge of the importance of tissue hypoxia and anoxia in the production of shock, it is obvious that bacterial infection must be considered in the mechanisms contributing to shock.

In this regard it is well to mention a gram-negative organism that only recently has been recognized for its shock-producing properties. During the past few years workers investigating extracorporeal mechanical hearts have isolated *Paracolobactrum aerogenoides* as an organism that occasionally may contaminate their mechanical systems and that will cause shock and very sudden

TABLE I. EFFECT OF CERTAIN BACTERIA ON THE OXYGEN-CARRYING CAPACITY OF RED CELLS AND HEMOGLOBIN*

Hemolytic *Staphylococcus aureus*	Hemolysis
Escherichia coli	No change or hemolysis
Clostridium welchii	Hemolysis
Hemolytic Streptococcus	Hemolysis, methemoglobin
Streptococcus viridans	Methemoglobin
Pneumococcus	Reduced hemoglobin
Anaerobic Streptococcus	Sulfhemoglobin, methemoglobin
Bacterium melaninogenicum	Hematin

*(After Altemeier, W. A.: Symposium on Shock, 1951.[26])

death to their animals upon intravascular injection.[31] It is resistant to many types of antibiotics and bactericidal substances, thus making the sterilization of the mechanical systems a matter of great concern. Such an organism, to date at least, is of no clinical importance.

THE POSSIBLE ROLE OF ANAEROBIC ORGANISMS IN THE PRODUCTION OF SHOCK

During the past ten years Fine and his co-workers[10] have been investigating the role of Clostridia in the relation of the response of animals to shock. After having worked out a well-controlled and repeatable method of bleeding unanesthetized dogs into a state of hypotension and irreversible shock, they were able to predict that 95 per cent of the dogs would die. By pretreating a series of such dogs with oral Aureomycin, they found that thirteen of the fifteen dogs so treated survived. They further studied the role of antibiotics (and, thus, bacterial infection) in shock by producing fatal hemorrhagic pancreatitis in dogs. This was done by injecting bile into the pancreas. They found that gas bacilli could be cultured from the pancreas in 70 per cent of the cases, and all animals died. When penicillin was given, 40 per cent survived, and when gas antitoxin was added, 60 per cent survived. When Aureomycin was given prophylactically 100 per cent of the animals survived.[10]

Indirect evidence of the importance and lethal effect of Clostridia infection following tissue anemia is found in the work of Markowitz,[33] who reported that the ordinarily fatal procedure of ligating the hepatic artery in dogs could be made relatively innocuous by treating the animals with large doses of penicillin or Aureomycin. This experiment has been repeated by others.[32] It is clear that the fatal clostridial infection that ordinarily follows hepatic artery ligation can be avoided by the proper antibiotic therapy. Thus animals that ordinarily would die in profound shock are saved by antibacterial therapy.

This experimental evidence strongly suggests that bacterial, and particularly clostridial, infection may well play a part in the production of certain types of shock. It is suggested that in the latter stages of shock, when the blood supply to the liver has diminished, anaerobic conditions may exist that allow the multiplication of Clostridia. It has been shown that these organisms may be present in the liver and only begin to function when such anoxic conditions are present. Clostridial growth yields exotoxins which have been shown to produce the signs and symptoms of shock. The obvious conclusion is that clostridial infection activated by the anaerobic condition found following hemorrhage or trauma may account for some of the later signs of shock. Fine[10] has suggested that the toxic factor VDM, supposedly produced by the anoxic liver, may be nothing more than clostridial exotoxins produced when the arterial supply to the liver is sufficiently diminished to allow relative anaerobic conditions to exist. In a like manner, he suggests that the resistance to trauma as shown in the Noble-Collip drum may be nothing more than an acquired active immunity to bacterial toxins, developed by the previously traumatized animals.

A serious objection exists to the transference of this experimental evidence from the dog to man. It is relatively easy to find the resting spores of anaerobes in the tissues of dogs, whereas in man this is not the case. The dog constantly

has Clostridia gaining access to his blood stream through the minute tears in his intestinal mucosa, subsequent to his eating small bones, roughage, etc. In man this presumably does not occur. Blind transference of data from an animal to a human being is never wise; this is particularly true when dealing with bacterial resistance. The evidence is suggestive, however, that anaerobic infection may complicate ordinary hemorrhagic or traumatic shock in situations where these organisms were not formerly suspected to exist.

SUMMARY

1. A review of some of the effects of trauma and hemorrhage on the circulatory system has been presented. Particular attention has been placed on the possible role played by the circulating toxins VEM and VDM.

2. Various types of experimental shock have been mentioned, including methods used in their production.

3. Some of the effects of pain, sedation, and anesthesia on the shocked individual have been reviewed.

4. The possible role of bacterial infection in the production of shock has been briefly reviewed. Attention has been drawn to recent work implicating anaerobic organisms as complicating factors in the toxemia found in profound shock.

REFERENCES

1. Cannon, W. B.: Traumatic Shock, New York, 1935, Appleton and Company.
2. Blalock, A.: Principles of Surgical Care, Shock and Other Problems, St. Louis, 1940, C. V. Mosby Company.
3. Blalock, A.: Experimental Shock. VI. Probable Causes for the Reduction in Blood Pressure Following Mild Trauma to an Extremity, Arch. Surg. 22: 598, 1931.
4. Parsons, E., and Phemister, D. E.: Hemorrhage and Shock in Traumatized Limbs, An Experimental Study, Surg. Gynec. & Obst. 51: 196, 1930.
5. Emerson, C. P., Jr., and Ebert, R. V.: A Study of Shock in Battle Casualties, Ann. Surg. 122: 745, 1945.
6. Beecher, H., Simeone, F. A., Burnett, C. H., Shapiro, S. L., Sullivan, E. R., and Mallory, T. B.: The Internal State of the Severely Wounded Man on Entry Into the Most Forward Hospital, SURGERY 22: 672, 1947.
7. Moore, F. E.: The Conquest of Space—By the Red Blood Cell, Ann. Surg. 135: 143, 1952.
8. Robertson, R., Trincher, I. H., and Dennis, E. W.: Intra-arterial Transfusions; Experimental and Clinical Considerations, Surg., Gynec. & Obst. 87: 685, 1948.
9. Grant, R. T., and Reeve, A.: Observations on the General Effects of Injury in Man. Medical Research Council Special Reports Series No. 277, London, 1951.
10. Fine, J.: Irreversible Shock. Symposium on Shock, Army Medical Service Graduate School, 1951.
11. Noble, R. L., and Collip, J. B.: A Quantitative Method for the Production of Experimental Traumatic Shock Without Hemorrhage in Unanesthetized Animals, Quart. J. Exper. Physiol. 31: 187, 1942.
12. Noble, R. L.: The Development of Resistance by Rats and Guinea Pigs to Amounts of Trauma Usually Fatal, Am. J. Physiol. 138: 346, 1943.
13. Chambers, R., and Zweifach, B. W.: Topography and Function of the Mesenteric Capillary Circulation, Am. J. Anat. 75: 173, 1944.
14. Zweifach, B. W.: Factors Regulating Blood Pressure. Transactions of Third Josiah Macy, Jr., Foundation, New York, 1949.
15. Chambers, R., Zweifach, B. W., Lowenstein, B. E., and Andlee, R. E.: Vaso Excitor and Depressor Substances as "Toxic" Factors in Experimentally Induced Shock, Proc. Soc. Exper. Biol. & Med. 56: 127, 1944.
16. Shorr, E., Zweifach, B. W., Furchgott, R. F., and Baez, S.: Hepato Renal Factors in Circulatory Hemostasis. IV. Tissue Origins of the Vasotropic Principles VEM and VDM Which Appear During Evolution of Hemorrhage and Tourniquet Shock, Circulation 3: 42, 1951.

17. Mazur, A., Litt, I., and Shorr, E.: The Relation of Sulfhydral Groups in Ferritin to Its Vaso Depressor Activity, J. Biol. Chem. **187**: 485, 1950.
18. Zweifach, B. W., Lee, R. L., Hyman, C., and Chambers, R.: Omental Circulation in Morphinized Dogs Subjected to Graded Hemorrhage, Ann. Surg. **120**: 232, 1944.
19. Van Slyke, D. D.: The Effects of Shock on the Kidney, Ann. Int. Med. **28**: 701, 1948.
20. Van Slyke, D. D.: Effects of Hemorrhage on the Kidney, Ann. New York Acad. Sc. **49**: 593, 1948.
21. Zweifach, B. W., Abell, R. G., Chambers, R., and Clowes, G. H. A.: Role of the Decompensatory Reactions of Peripheral Blood Vessels in Tourniquet Shock, Surg., Gynec. & Obst. **80**: 593, 1945.
22. Kniseley, M. H., Eliot, T. S., and Block, E. H.: Sludged Blood in Traumatic Shock. Microscopic Observations and Precipitation and Agglutination of Blood Flowing Through Vessels in Crushed Tissues, Arch. Surg. **51**: 220, 1945.
23. Overman, R. R., and Wang, S. C.: The Contributory Role of the Afferent Nervous Factor in Experimental Shock; Sublethal Hemorrhage and Sciatic Nerve Stimulation, Am. J. Physiol. **148**: 289, 1947.
24. Wang, S. C., Painter, E. E., and Overman, R. R.: The Mechanisms of Prolonged Fluorescein Circulation Time in Experimental Traumatic Shock, Am. J. Physiol. **148**: 69, 1947.
25. Powers, S., Reed, C., and Gregersen, M. I.: The Effects of Morphine on Dogs in Hemorrhagic and Traumatic Shock, Am. J. Physiol. **148**: 269, 1947.
26. Altemeier, W. A.: Infections as a Factor in the Cause of Shock. Symposium on Shock, Army Medical Service Graduate School, 1951.
27. Andrews, E., and Harkins, H. N.: "Surgical Shock." Factors in Pneumonia, Ann. Int. Med. **10**: 1503, 1937.
28. Ebert, R. V., and Stead, E. A., Jr.: Circulatory Failure in Acute Infections, J. Clin. Investigation **20**: 671, 1941.
29. Janeway, T. C.: Some Common Misconceptions in the Pathological Physiology of the Circulation and Their Practical Significance, New York J. Med. **85**: 193, 1907.
30. Green, H. N.: Shock Producing Factors From Striated Muscle, Lancet **2**: 147, 1943.
31. Nelson, R. M.: Metabolic Effects of Paracolon Bacillus, Ann. Surg. **134**: 885, 1951.
32. Tanturi, C., Swigart, L. L., and Canepa, J. F.: Prevention of Death From Experimental Ligation of the Liver (Hepatic Proper) Branches of the Hepatic Artery, Surg., Gynec. & Obst. **91**: 680, 1950.
33. Markowitz, J., Rappaport, A., and Scott, A. C.: Prevention of Liver Necrosis Following Ligation of Hepatic Artery, Proc. Soc. Exper. Biol. & Med. **70**: 305, 1949.

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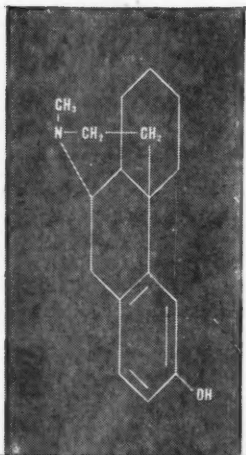

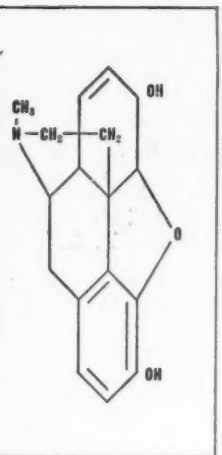

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SIDE EFFECTS	DROMORAN *Dose: 5 mg (1/12 gr) Pain Relief: 5 to 8 hrs	MORPHINE *Dose: 15 mg (1/4 gr) Pain Relief: 4 to 6 hrs
diminished urine	rare	frequent
constipation	rare	frequent
disorientation	rare	frequent
depressed appetite	rare	frequent
nausea	less	occasional
vomiting	less	occasional

Caution: Dromoran is a narcotic analgesic. It has addiction liability equal to morphine and for this reason the same precautions should be taken in administering the drug as with morphine.

DROMORAN®—brand of methorphinan (dl-3-hydroxy-N-methyl-morphinan)

**Average dose*

DROMORAN

(dl) Hydrobromide

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